RANDOMISED CONTROLLED TRIAL OF CTG VERSUS CTG+ST – A SWEDISH MULTI CENTRE TRIAL.

Appendixes

1 INTRODUCTION

Intrapartum fetal surveillance is still under debate, despite 30 years of clinical experience and numerous clinical trials. In spite of the anticipation in the early 1970's of a marked decrease in the cerebral palsy with the introduction of electronic fetal monitoring, we have found trends of the opposite with increasing cerebral palsy in term babies [1]. The medico-legal situation in some countries has made obstetrics a most problematic area and the argument is sometimes raised of the value of intrapartum fetal monitoring [2]. High operative delivery rates for suspected intrapartum hypoxia has become a major concern and there is a trend away from electronic fetal monitoring.

We presently use subjective (and poorly predictive) analysis of the continuous fetal heart rate but the fetal ECG, which is easily obtained in labour, contains more useful information that can be quantified objectively. Under these circumstances, there is a need to look for improvements in intrapartum fetal assessment and waveform analysis of the fetal electrocardiogram has emerged not as an alternative to cardiotochography but as a support tool to allow more accurate interpretation of intrapartum events.

1.1 The ST Waveform of the Fetal ECG - Experimental data

The ECG reflects the summation of electrical events within the myocardial cell, as seen from the body surface. The ST waveform of the ECG represents re-polarisation of the myocardial cells and is particularly sensitive to metabolic events, in particular situations with coronary insufficiency and myocardial ischemia during exercise testing. Although it is of proven value in the adult, detailed knowledge is required about the fetal situation before waveform analysis could be applied during human labour. Basically, during hypoxia, the fetus is utilising a series of defence mechanisms, including decreased non-essential activity, increased tissue oxygen extraction, increased sympathetic activity, redistribution of blood flow and anaerobic metabolism [3]. Among these, the increase in sympathetic activity, with an increase in circulating adrenaline, activates the myocardium with an increase in workload (the product of cardiac output, myocardium contractility and blood pressure). This increase in workload during hypoxia has been shown to be directly related to the increase in T-wave height, quantified by the T/QRS ratio, $r = 0.73$, $p < 0.01$ [4]. Under these circumstances, the ability of the fetus to maintain aerobic metabolism in the heart depends on the ability to increase coronary oxygen flow and oxygen extraction. If there is an imbalance between myocardial oxygen supply and consumption, determined by the workload, then anaerobic metabolism, with a breakdown of myocardial glycogen stores starts. The glycogenolysis has been related to the increase in T wave height in both the mature guinea pig fetus [5] and the mature fetal sheep [6] and occurs in parallel with the fetal adrenaline surge [7]. There is little doubt that during acute hypoxia, the term, appropriate grown, sheep and guinea pig fetuses display reproducible changes in the ST wave form, quantified by the

T/QRS ratio[8, 9, 10]. Identical ST waveform changes will emerge as a consequence of an increase in myocardial performance during beta adrenoceptor activation by the infusion of beta mimetic drugs [11].

ST depression with negative T waves has been observed during hypoxia experiments in experimentally growth retarded guinea pigs whilst their normally grown littermates showed ST elevation [12]. Such runted fetuses have lower catecholamine levels and probably have depleted myocardial glycogen reserves and a blunted sympathoadrenal response. During hypoxia they are likely to have ineffective anaerobic metabolism and suffer the direct effect of oxygen lack in the deeper myocardial layers (endocardium) before the superficial layers (epicardium) to alter the sequence of repolarisation to produce a negative ST wave form - the ischaemic pattern in the adult.

Thus, the pathophysiology of ST waveform change have been well studied over the past 20 years in a series of experiments on the fetal guinea pig and lamb. These findings have stimulated the development of a dedicated fetal ECG monitor - STAN (Neoventa Medical AB, Göteborg, Sweden) incorporating both standard CTG and ST waveform analysis [13]. The STAN concept has now been taken through the process of recognised validation including several prospective studies [14] and a large randomised trial in Plymouth of 2400 high risk, term deliveries [15].

1.2 Plymouth Randomised Trial

This is the first randomised controlled trial where 2,400 high-risk term deliveries have been studied comparing CTG + ST waveform analysis with standard CTG monitoring.

The trial has tested the hypothesis that the combination of ST wave form and CTG analysis compared with CTG analysis only would reduce operative interventions for fetal distress without placing the fetus at a risk.

There was a highly significant reduction of 46% in operative deliveries for fetal distress in the ST + CTG arm with no difference in operative deliveries for other reasons. A retrospective analysis of the CTG showed operative deliveries for fetal distress in 2.7% of cases with normal CTG in the CTG only group, as compared with 0.3% in the STAN group. Cases with an intermediate CTG pattern had operative interventions in 19.5% and 9.6%, respectively, and with an abnormal CTG the intervention rate was 44.4% and 35.3%, respectively. 43% of operative interventions were judged unnecessary in the CTG arm as compared with 5% in the STAN arm of the trial.

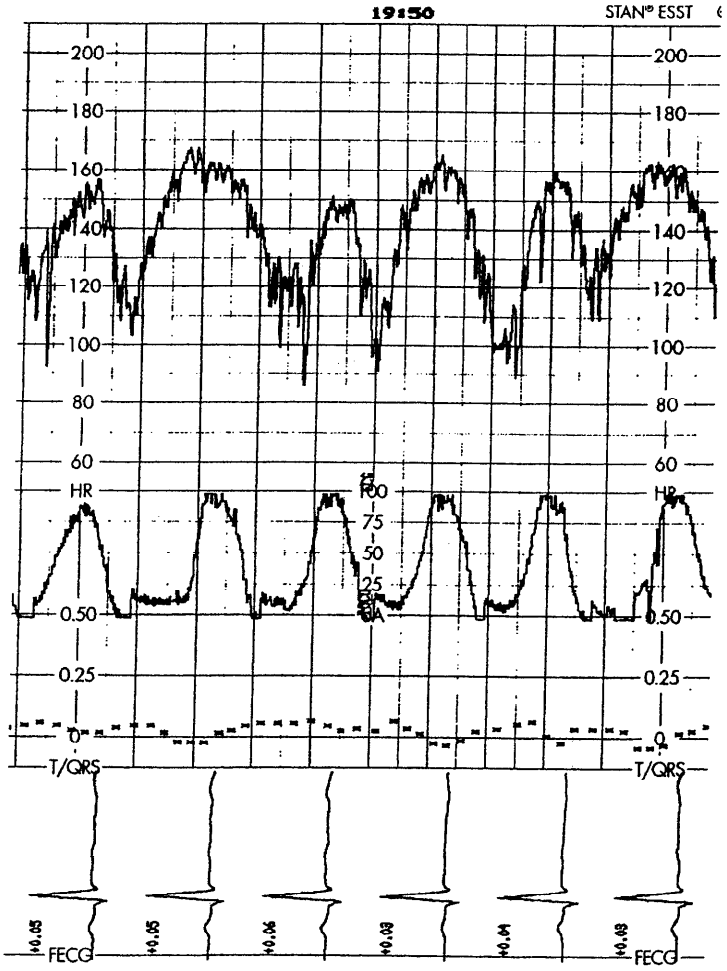
There were no significant differences in the measures of neonatal outcome, but fewer low 5 minute Apgar scores (20 versus 32, p=0.12) and less metabolic acidosis (5 versus 13, p=0.09) in the ST + CTG arm were apparent. There was also a significant reduction in the use of fetal blood sampling. Eighteen percent of abnormal traces in the CTG arm should have had an intervention (2 cases of asphyxia) as compared with 9% in the STAN arm (1

case of asphyxia). This last case displayed biphasic/ negative T waves that were missed by the staff. To reduce the likelihood of this to be repeated, the new STAN recording system includes an automatic identification of abnormal ST segment patterns to complement that already existing as the ration between T and QRS amplitudes (T/QRS ratio).

1.3 The STAN system

The step from the experimental to the clinical phase involved the design of an appropriate system for signal acquisition, including aspects such as ECG lead configuration, appropriate signal bandwidths [13] and validation of scalp electrodes [16]. The mode of data presentation is illustrated in Figure 1.

Figure 1



Fetal Heart Rate

Uterine activity

T/QRS ratio

Average ECG complexes with corresponding T/QRS ratio

Automatic detection of biphasic waveforms.

Apart from an ordinary CTG, averaged ECG complexes are displayed every two minutes. The T/QRS ratio is plotted for every 30 beat ECG average. Although in principle the STAN monitor has been the same since its introduction in 1989, a constant development of both hardware and software to improve signal quality and the identification of appropriate ECG signals for

waveform analysis has allowed considerable improvements. The current system, using digital signal processing, allows for detailed ST analysis throughout labour.
Furthermore, to assist the staff the computer automatically generates a ST event-log file. The operator could retrieve this file during the recording and have the stored data displayed. This Expert System ST (ESST) is only using the information already available on the STAN printout but summarises in verbal terms any changes that might have occurred together with a signal quality assessment.

1.4 Purpose of trial

The Plymouth trial focused on the ability of the then newly developed STAN system to safely reduce the number of operative interventions for fetal distress. This primary aim was fulfilled but an issue was raised regarding the ability of the staff to consistently assess the ST waveform (17). Obviously, dedicated training has to be applied whenever a new medical device is made use of. However, it would be advantageous if the recording system per se would be able to facilitate data interpretation. This has now been achieved by the use of a computerised (PC-based) STAN ESST system to include the following aspects:

1. Enhanced signal processing to eliminate as much as possible signal noise.
2. Automatic detection of biphasic ST segment waveforms.
3. Automatic generation of an event-log file that stores any relevant ST waveform changes. To obtain support in the interpretation of the ST data, the user could address this file and obtain a verbal statement on the extent of any ST waveform changes.
4. A multi-media based, interactive teaching and training module.

The question to be asked is to what extent the recent developments would support the safe clinical use of the ST waveform model of intrapartum fetal surveillance not only reducing intervention rates caused by changes in the fetal heart rate pattern but also reduce perinatal morbidity.

2 STUDY OBJECTIVE

Primary aims:

- to reduce perinatal morbidity as identified by a significant cord artery metabolic acidemia (pH ≤7,05 and BDecf ≥12.0 mmol/l).

Secondary aims:

- to evaluate the use of CTG and ST waveform protocols and guidelines in clinical practice.
- to reduce operative interventions.
- to undertake cost-benefit analysis.

3 STUDY DESIGN

3.1 Studied group

Women will be approached at the time the decision to use a fetal scalp electrode is made and their informed consent obtained. Only single spiral electrodes will be used for the duration of the study.

The primary aim of the trial to demonstrate at least a 50% reduction in the number of cases with metabolic academia, defined as pH ≤ 7.05 and BDecf ≥12.0 mmol/l, with a power of 80% and a test performed on the 5% level.

The initial size of the trial is based on the assumption of a similarity between the incidens of cord artery metabolic acidaemia in the Plymouth and the current Swedish multi centre trial cohort of 13/1000 deliveries monitored using a fetal scalp electrode (15). Furthermore, we also assume a 70% reduction in the incidens. To fulfil the primary aim applying these figures, the size of the trial would have to be 3200 cases. If the reduction of cases with metabolic academia will only be 50% then the size of the trial would have to increase to 7200 cases.

An interim analysis of the trial data should take place after 1600/2 = 800 cases have been recorded in each arm. The final size of the trial will be based on the outcome of this analysis.

The basic model of CTG and ST + CTG monitoring has not changed when comparing the Plymouth trial and the current Swedish multi centre trial. Thus, it would be appropriate to conduct a meta analysis combining the two sets of data.

3.2 Entry criteria

All pregnancies with a cephalic presentation at 36 completed weeks of gestation that are monitored during active labour using a fetal scalp electrode.

3.3 Exclusion criteria

Women who deliver so rapidly after arrival in the labour ward that less than 30 minutes of first stage or only second stage recordings are obtained.

The lag time between end of recording and delivery must not exceed 20 minutes.

The reason for these exclusions is to provide an opportunity for the monitoring system to stabilise itself and to obtain data of a sufficient quantity and quality to allow for high quality fetal assessment.

Women using TENS, as signal quality may be seriously impaired while TENS is being used as an on-going method of analgesia.

Pregnancies where a gross fetal abnormality is recognised prior to labour.

4 INFORMED CONSENT

The patients will have been given some previous information on the trial so that they will be aware of the study taking place on the labour wards and its general objectives. This information will be given at the antenatal clinic.

Before admission to the study, all patients will be informed of the nature of the study, its purpose, procedures and the benefits and risks involved in study participation. Each patient will be given the opportunity to ask questions and will be informed about the fact that they are free to withdraw from the study at any time.

Patient information sheet: Appendix 1.

5 RANDOMISATION AND METHOD

5.1 Randomisation

Allocation will be made randomly using a computerised technique whereby each recorder at *power-on* will allocate itself to become either a standard CTG recorder or a CTG+ST recorder. 50 % are allocated to the CTG only group (control group) and the rest to the CTG+ST group.

5.2 Method

With the fetal scalp electrode applied to the presenting part of the fetus, the fetal electrocardiogram signal will be monitored throughout labour in both groups. The CTG group (control group) will be managed according to standard CTG-based practice (see below 5.3, Classification of Intrapartum CTG).

In the control group STAN recorders will be used with blinded ST analysis.

The ST + CTG group will be managed according to CTG + ST clinical guidelines (see below 5.4, Classification of ST waveform). The classification of the traces in both groups is to be made continuously and main indications of obstetric interference and time of interference written down (vivid notes) on

specific form to follow in patient record form. These measures do prepare for a blinded assessment of the recordings. The fetal ECG and uterine activity signals are stored in a "raw" data format.

All patients entering the study will have the cord artery and vein acid-base status assessed. The cord should be double-clamped as soon as possible after birth of the baby (before the placenta is delivered) and using preheparinized syringes or capillary tubes the blood is obtained from both artery and vein. An alternative is to puncture the artery and vein directly at delivery.

Acid-base status should be analysed within 4 minutes or if placed on ice, within 20 minutes.

5.3 Classification of Intrapartum CTG (See Appendix 3.)

Normal CTG

- At least 2 accelerations (>15 beats for 15s) in 20 min.
- Basal heart rate 110-150.
- Heart rate variability (bandwidth) 5-25 bpm.
- No decelerations (except early decelerations and uncomplicated variable decelerations in late first stage of labour).

Intermediate CTG.

- Absence of accelerations for >40 min.
- Basal heart rate 100-110 or 150-170 bpm (normal baseline variability, no decelerations)
- Heart rate variability (bandwidth) <5 bpm, > 40 min (normal baseline, no decelerations)
  >25 bpm in the absence of accelerations
- Mild variable decelerations (depth<60 bpm, duration <60 s).
- Occasional transient prolonged bradycardia if heart rate drops to<80 bpm for 2 min or > 3 min if < 100 bpm.

Abnormal CTG

- Baseline heart rate >150bpm + silent pattern and/or repetitive late or variable decelerations.
- Silent pattern (heart rate variability < 5 bpm) for > 60 min.
- Complicated variable decelerations (>60 dropped beats for >60 seconds duration) and changes in shape or loss of variability in or between contractions, slow recovery.
- Combined/biphasic decelerations (variable followed by late).
- Prolonged bradycardia (FHR < 100bpm) for > 10 min with no sign of recovery.
- Repeated variable decelerations.
- Repetitive late decelerations.

Preterminal CTG

- Total loss of FHR reactivity and variability with or without decelerations.
- Sinusoidal pattern with no accelerations.

5.4 Classification of ST waveform

The STAN ESST system contains automatic assessment of signal quality according to the following;

1. Good quality signifies a signal that will provide a stable fetal ECG throughout labour, optimal signal amplitude with little noise.

2. Intermediate quality. A signal that would work but where there is some likelihood of the signal quality to deteriorate as labour continues.

3. Poor signal quality. Signals that may work only for fetal heart rate assessment. The operator will be recommended to check electrodes.

The existence of a maternal ECG signal is automatically detected at start-up. All statements on signal quality will be presented on screen and paper.

The operator should at start-up check for signal quality statements and aim to identify the rare occasions when immediate action is required

The continuous paper printout and the PC-screen provide help to identify changes in T/QRS ratios and the occurrence of biphasic ST waveforms. Furthermore, the operator will have access to a "help" function that activates the event log file to give an automatic assessment of the extent of ST changes over time. Clinical action is made according to the CTG + ST clinical guidelines.

5.5 Fetal scalp pH guidelines

pH	<7.20	Abnormal – immediate delivery should be considered.

The reason for clinical action should be noted prospectively with order of priority of indications stated.

5.6 Management CTG group

Assessment over 15 minutes.

- Clinical action in cases of intermediate and abnormal CTG will follow standard guidelines (see Appendix 3). If, after correction of
- maternal hypotension
- uterine hypertonus
- exclusion of cord compression

- allowance for local anesthetic absorption effects after an epidural the CTG abnormality persists, a fetal scalp sample will be taken.

In cases where the trace is considered to be preterminal (i.e. a persisting severely abnormal trace) direct recourse to immediate delivery may be taken without scalp sampling.

5.7 Management STAN/CTG group (See also appendix 4.)

Assessment over 15 minutes.

St waveform + CTG clinical guidelines

	ST waveform		
CTG	Normal	High & Stable	Negative or Raising
Normal	No action	No action	FBS or deliver[1]
Intermediate	No action	No action	Deliver[2]
Abnormal	See note 4	Deliver	Deliver[3]

STAN® clinical guidelines for action with a mature fetus (≥ 36 weeks).

During the recording use the printed ECG complexes to monitor signal quality and to assess waveform shape. Be aware that biphasic ST waveforms are abnormal and may give a normal T/QRS value.

1. Negative/Biphasic ST - T/QRS less than -0.05 for more than 20 minutes. Rising -T/QRS rises more than 0.40 over 15 minutes, expedite delivery without FBS.

2. Negative/Biphasic ST - T/QRS less than -0.05 for more than 20 minutes. Rising - T/QRS rises more than 0.15 from the base line level over 15 minutes.

3. Any negative or bisphasic ST changes as well as any T/QRS increase over 5-10 minutes.

4. FBS should be repeated every hour or earlier. If an FBS is not available, intervention can be delayed until the CTG shows evidence of deterioration.
   - Loss of short term variability (band width less than 5 bpm)
   - Progressive tachycardia or bradycardia
   - Decelerations become wider and deeper
   - Overshoot accelerations following decelerations

If the CTG remains unchanged but the ST waveform shows an acute change, as identified under p.3, delivery should also be expedited.

Note: A "preterminal" CTG should always cause immediate delivery. No need for additional ST waveform analysis.

Repeat scalp samples after 15 – 30 minutes if any signs of a further deterioration occur.

5.8 Considerations of second stage of labour

The first and second stages of labour will be analysed separately.
During second stage there will be situations where a new scalp electrode should be applied if the trace is of poor quality.
Second stage presents a more dynamic situation compared to first stage and requires a close surveillance. A persistent change in ST waveform over a 5-minute period should be regarded as abnormal.

5.9 End points

1. Both the cord acid-base status and the condition of the neonate will be used to assess the accuracy of obstetric intervention. Biochemical morbidity cut-off points indicating an umbilical artery acidaemia is a pH ≤7.05 and a base deficit in extracellular fluid of ≥12.0 mmol/l. The cord acid-base analysis will also include a comparison between cord artery and vein data. If a difference in cord artery and vein base deficit, the artery should reflect more acutely emerging changes whereas the vein base deficit should reflect the more basal condition of fetal acid-base balance. The extent to which such acid-base differences are reflected in the CTG and ST parameters will also be tested.

   The Expert DataCare software developed by Jon Garibaldi, PhD, University of Plymouth will be used to assess the accuracy of cord acid-base data.

2. Change in neonatal morbidity as identified by the following parameters;
   – Apgar at 5 min 4–6 and 0-3.
   – Assisted ventilation 3-5 min and >5 min.
   – Admittance to special care baby unit
   – Neonatal seizures or other neurological abnormalities.

3. Change in the frequency of operative delivery due to fetal distress separated into groups depending on cause of operative delivery and mode of delivery.

4. Test for gender differences.

5. Validation of how the event log file based information in the CTG-only group retrospectively would effect the clinical activity.

6. Change in the relative frequency of normal to abnormal scalp pH.

5.10 The neonate

1371

All babies will have the usual assessment of condition at birth and within 48 hours recorded. In cases with signs of neonatal morbidity;

- 5 min Apgar <7

- assisted ventilation >3 mins
- neurological abnormalities during the neonatal period
  (see SCBU form in Appendix 5)

The clinical research workers according to SCBU form (see Appendix 5) will make a detailed account of neonatal condition and progress.

5.11 Retrospective, blinded review of traces and clinical management in relation to the trial protocol

This will take place accordingly:

- Each case will be presented to a reviewer using the STAN trainer module and assessments will be made in 30 minute segments.
- CTG will be classified as normal, suspicious or pathological.
- The ST waveform will be classified from:
  a) the reviewers statement
  b) the event-log file.

This analysis will identify to what extent the study protocol was followed clinically. Furthermore, the study design allows for a retrospective analysis of CTG+ST in those cases also where clinical action was based on CTG only.

6 DATA PROCESSING

6.1 Case record form

See Appendix 5.

6.2 Data disposition

For each patient, data will be recorded according to a fixed form. On request copies of the case record form and ECG signal recordings will be forwarded to the responsible investigator and monitor.

6.3 Statistical analysis

An interim analysis of the data should be made after 1600 cases. If, at this point in time the incidens of metabolic acidaemia is found to be incorrect an expansion of the trial beyond 3200 cases should be considered.

7 ADMINISTRATIVE PROCEDURES

7.1 Ethical committee approval (Appendix 6)

This study will only be undertaken when full approval of the protocol has been obtained from the appropriate hospital and the sponsor receives a copy of the approval.

7.2 Investigator indemnification (Appendix 7)

7.3 Personnel

Personnel taking part in the study are listed in Appendix 8.

7.4 Economy

The costs for the study will be agreed upon in a separate contract.

7.5 Study report and publication

A preliminary report of the statistical evaluation should be made after 1600 cases by the investigators in co-operation with the monitor at Neoventa Medical AB.

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Appendix 1

Monitoring of your baby during delivery

To guarantee the highest possible quality of care for both the mother and child there is need for constant development and improvements of fetal monitoring techniques. We know the electrical signal from your baby's heart, the ECG, may provide additional information. A research project is currently undertaken at the labour ward to validate this new source of information. We would like to invite you to participate in this important work. Of course your participation is on a voluntary basis.

At some stage during labour, your midwife or doctor, may want to keep an eye on your baby's heartbeat more closely by attaching a small clip, called a fetal scalp-electrode, to your baby's head. This clip on the baby's head actually records the electrical signals from the baby's heartbeat. These signals are called the electrocardiogram or ECG and it is from this that the baby's heart rate is calculated.

A group of scientists both in Sweden and England have studied the fetal ECG and shown that the combined analysis of fetal heart rate and ECG provides an opportunity to improve the information from the baby during birth. As a joined effort between the labour wards in Gothenburg, Lund and Malmö, a research project is currently undertaken to document to what extent the combined analysis of fetal heart rate and fetal ECG-analysis will improve our ability to monitor the baby. Thus, the common mode of fetal monitoring, i.e. the CTG, is compared with a new mode where the CTG is combined with fetal ECG waveform analysis. A computer is used to assist in the interpretation of fetal ECG changes.

At the time when scalp-electrode may be considered you will be asked if you would like to participate in the investigation. The only extra that will happen is the application of a skin electrode on your thigh. In half of the cases, the standard information, the CTG, will be shown to the midwife and the doctor, and in the other half both the CTG and the fetal ECG waveform analysis will be shown. The computer will decide and there is no way that decision could be changed.

The study should not cause any harm or be of any nuisance to you. Obviously labour is always a high-risk situation and that is the reason why the baby is monitored. However, there is nothing to show that the combined analysis of CTG and fetal ECG waveform increase the risk. In the study, basic information regarding your pregnancy, delivery and the condition of the child will be collected. The information is the same as already collected for your hospital notes. Full secrecy will apply to the data.

If, for any reason, you do not wish to participate, we will simply use the standard CTG-recorder.

Your midwife and doctor are pleased to answer any question you may have.

Responsible physicians: Dr. Håkan Norén, Doc. Henrik Hagberg, Doc. Lars-Åke Mattsson, Doc. Håkan Lilja
Kvinnokliniken SU/Östra
416 85, Göteborg
tfn. 031-343 40 00

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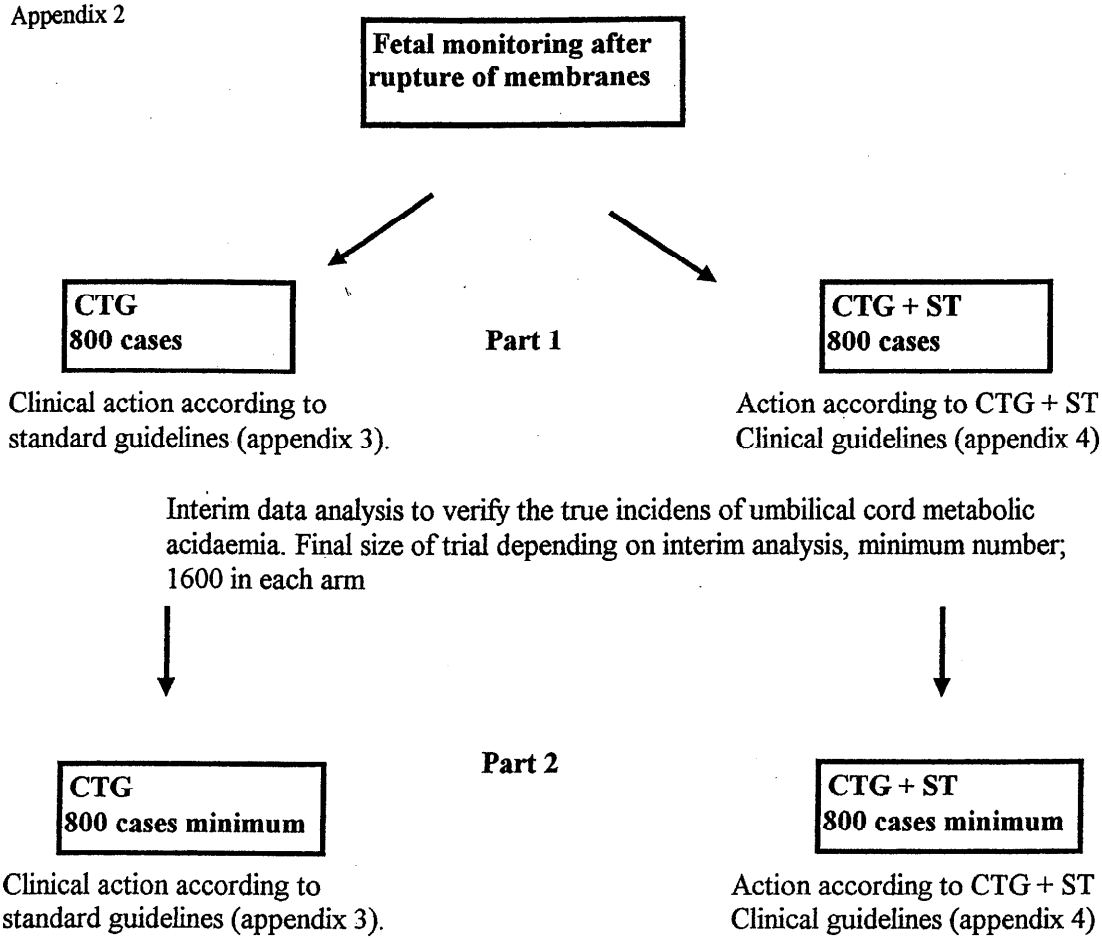
Appendix 2


Fetal monitoring after rupture of membranes
CTG
800 cases
Part 1
CTG + ST
800 cases
Clinical action according to standard guidelines (appendix 3).
Action according to CTG + ST Clinical guidelines (appendix 4)
Interim data analysis to verify the true incidens of umbilical cord metabolic acidaemia. Final size of trial depending on interim analysis, minimum number; 1600 in each arm
CTG
800 cases minimum
Part 2
CTG + ST
800 cases minimum
Clinical action according to standard guidelines (appendix 3).
Action according to CTG + ST Clinical guidelines (appendix 4)

Appendix 3

CTG based management

CTG classification

First stage of labour	Baseline heart rate	Heart rate variability	Decelerations	Action
Normal	110 - 150 bpm	5 – 25 bpm	Early decel or uncomplicated variable decel during the later part of first stage of labour	Continue the recording
Suspicious	100 – 110 bpm 150 – 170 bpm	a. >25 bpm and no accelerations. b. <5 bpm >40 min. c. no accelerations for >40 min.	Variable decel. Transient bradycardia, return to baseline within 2-3 min.	FBS if CTG not normal in 1 hour
Pathological	> 150 bpm + reduced variability and/or late or variable decel.	<5 bpm for > 60 min Sinusoidal pattern with no accelerations	Repetitive late -. Complicated variable - combined / biphasic Prolonged bradycardia	FBS to provide clinical guidance
Preterminal	Complete loss of variability and reactivity, with or without decelerations			Deliver
Second stage of labour Patological	>150 bpm + reduced variability and/or late or complicated variable decel. Progressive bradycardia, baseline heart rate <100 bpm and decreasing gradually between contractions. Persistent bradycardia, <80 bpm.			Deliver

Appendix 4

CTG + ST, simplified interpretation model

A. Findings in favour of assisted delivery or a scalp blood sample

	CTG normal	CTG suspicious	CTG pathological
T/QRS increase	>0.25	>0.15	>0.10
Neg T/QRS	>20 min	>20 min	episodic
Biphasic ST	-	BP 3, >20 min	repeated BP 2+3

-

-

A preterminal CTG will always call for action

B. Findings in favour of a continuation of labour

	CTG normal	CTG suspicious	CTG pathological
ST normal	yes	yes	yes if <90 min and stable CTG alt scalp blood sample
ST high and stable	yes	yes	no

Appendix 5

CASE RECORD FORM (CRF)

Randomised controlled trial CTG versus CTG + ST – a Swedish multi centre study.

Responsible investigator:

Signature:

Investigators:

Signatures:

Study Subject No: _____
Initials: _____
Date of birth: _____ _____ _____
year month day

All patients have obtained information consent regarding the list of points.

Monitor´s address: K G Rosén
Neoventa Medical AB
Medicinaregat 3A
SE413 46 Göteborg
Sweden

Check patients:
- understand this is a trial
- purpose
- procedures involved and differences from standard cases
- randomisation explained
- informed consent obtained.

Date: _____ _____ _____ _____
year month day Investigator´s signature

BACKGROUND DATA

Date ___ ___ ___

Patient ID ___ ___ ___

Date of birth ___ ___ ___

Parity ___

1 Alive at 28 days
2 Neonatal deaths
3 Stillbirths

Best estimate of gestational age
(completed weeks) ____

Confirmed by ultrasound
between 16 and 24 weeks ___

1 Yes
2 No

Antenatal complications ___

1 Normal
2 Proteinuric pre-eclampsia
3 Diabetes
4 Suspected IUGR
5 Antepartum haemorrage
6 Others

Drugs in pregnancy (Specify generic names) _____

LABOUR PHASE

Presentation ___

1 Cephalic
2 Breech

Onset of labour ___

1 Spontaneous
2 Induced

Time of onset of labour (D, H, M) ___ ___ ___

Rupture of membranes ___

1 Spontaneous
2 Artificial

Time of membrane rupture (H, M) ___ ___

Liquor ___

1 Clear
2 Meconium
3 None

Drugs ___

1 Oxytocin
2 PG
3 Both

Analgesia for labour ___

1 None
2 TENS
3 Pethidine
4 Epidural
5 Others (specify) _____

Time first given (day, hour, minute) ___ ___ ___ ___ ___ ___

CTG record (time of onset) ___ ___

STAN record

Time begun ___ ___
Time ended ___ ___

Reason for FBS _____

FBS:	**First**	**Second**	**Third**
Time (H, M)	___ ___	___ ___	___ ___
Cx dil	___ ___ ___	___ ___ ___	___ ___ ___
___ ___ ___		___ ___ ___	___ ___ ___
pCO_2	___ ___ ___	___ ___ ___	___ ___ ___
pO_2	___ ___ ___	___ ___ ___	___ ___ ___
BE (ecf)	___ ___ ___	___ ___ ___	___ ___ ___

pH

Time start second stage ___ ___

Time of delivery ___ ___

Mode of delivery ___

1 SVD
2 Ventouse, for rotation
3 Ventouse, non-rotation
4 Forceps, for rotation
5 Forceps, non-rotation
6 Ceasarian, epidural
7 Ceasarian, general anaesthesia

Reason for operative delivery ___

1 Abnormal CTG

2 pH
3 Failure to progress
4 Other
5 Abnormal ECG waveform (specify) _____

_____

ADDITIONAL DATA

Complications of delivery (specify) _____

Birth weight, grams ____

SGA ___
1 Yes
2 No

Sex ___
1 M
2 F

Placental weight (if available), grams ____

Cord Arterial
pH ___
pCO_2 ___
pO_2 ___
BE (ecf) ___

Cord Vein
pH ___
pCO_2 ___
pO_2 ___
BE (ecf) ___

Data checked by Expert DataCare ___
1 Yes
2 No
Classification code: _____

Apgar scores
1 min ___
5 min ___
10 min ___

Time to first breath (min) ___

Resuscitation ___
1 Yes
2 No
Time of onset (min after delivery) ___
Duration (min) ___
Method ___
1 Facemask only
2 IPPV

Drugs for resuscitation (specify) _____

Admission to SCBU? ___

1 Yes

2 No

If "yes", continue on separate SCBU form.

SPECIAL CARE UNIT (SCBU) FORM

Age when admitted to SCBU (D, H, M) ___ ___ ___

Reason ___

1 Asphyxia
2 Hypothermia
3 SGA
4 Congenital abnormality - specify
5 Apnoea / Cyanosis
6 Others - specify

First neonatal blood gas

Time (H, M) ___ ___

Route ___

1 Capillary
2 Arterial
3 UA catheter

pH ___ ___ ___

pCO_2 ___ ___ ___

pO_2 ___ ___ ___

BE (ecf) ___ ___ ___

Blood glucose ___ ___ ___

Respiratory support (day)	1	2	3	4	5	6	7
	___	___	___	___	___	___	___

1 None
2 O_2 alone
3 CPAP
4 IPPV

Reason for respiratory support ___ ___	1	2	3	4	5	6	7
	___	___	___	___	___		

1 Apnoea
2 Cyanosis
3 Other (specify)

Sedation (day) ___ ___	1	2	3	4	5	6	7
	___	___	___	___	___		

1 Yes
2 No

Neorology

Reactivity (day) ___ ___	1	2	3	4	5	6	7
	___	___	___	___	___		

1 Normal

2 Apathy
3 Hyperexitable

Seizures (day) 1 2 3 4 5 6 7

__ __ __ __ __ __ __

1 None
2 Focal
3 General

	1	2	3	4	5	6	7
Tonus	__	__	__	__	__	__	__

1 Normal
2 Hypotonic
3 Hypertonic

Hypoglycaemia __

1 Yes
2 No

Lowest blood glucose _____

Main feeding pattern (day whilst in hospital)	1	2	3	4	5	6	7
1 Breast	__	__	__	__	__	__	__
2 Bottle	__	__	__	__	__	__	__
3 Tube	__	__	__	__	__	__	__
4 IV	__	__	__	__	__	__	__

Cerebral ultrasonographic examination __

1 Yes
2 No

Computerised tomography __

1 Yes
2 No

Date of discharge from SCBU (M, D) __ __

Date of discharge from hospital (M, D) __ __

Diagnosis on discharge (specify) _____

Paediatric follow-up __

1 Yes

CURRICULUM VITAE

Appendix 8

Surname:	**Maršál**
First name:	**Karel**
Date and place of birth:	[redacted]
Residence:	Malmo, Sweden
Address:	Department of Obstetrics and Gynecology, University Hospital Lund, S-221 85 Lund, Sweden
Education:	
Undergraduate 1960-1967	Faculty of Medicine, Charles University, Prague, Czechoslovakia
Postgraduate	
1969-1977	University Hospital Malmo, University of Lund, Malmo, Sweden
1977	Specialist in Obstetrics and Gynecology, Swedish Board for Postgraduate Medical Education
1973-1977	Research student, Faculty of Medicine, University of Lund, Sweden
1977	PhD thesis "Fetal Breathing Movements in Man"
Major appointments:	
1984-1997	Head of the Obstetric/Perinatal division, University Hospital Malmö
1991-1997	Professor, University of Lund, Department of Obstetrics and Gynecology, General Hospital, Malmö, Sweden
1995-	Honorary Guest Professor, Charles University, Prague, Czech Republic
1997-2000	Director of undergraduate studies (phase II), Faculty of Medicine, University of Lund, Sweden
Current appointments	
1997-	Professor, Chairman, University of Lund, Department of Obstetrics and Gynecology, Lund, Sweden
2001-	Head of the Clinical Department of Obstetrics and Gynecology, University Hospital, Lund, Sweden
Awards:	Honorary member: - Italian Society of Obstetrics and Gynecology - Czech Society of Obstetrics and Gynecology - Yugoslavian Society of Ultrasound - Russian Society of Gynecological Oncologists - Royal College of Obstetricians and Gynaecologists (Fellow ad eundem) Medal – 650 years Jubilee of Charles University, Prague (1998) Ian Donald Gold Medal (ISUOG 2000) Drs. Haackerts Gold Medal in Prenatal Medicine (2001)
Offices held:	
1986-	Secretary of the Southern Swedish Society of Gynecology
1991-1997	President of the Swedish Society of Medical Ultrasound
1991-1998	Board of Directors, European Federation of Societies of Ultrasound in Medicine and Biology,
1998-	European Committee for Medical Ultrasound Safety
1997-	Delegate for Sweden, European Association of Perinatal Medicine (EAPM)
1996-	Chairman, Study Group for Standardization of Birth Certificates (EAPM)
1991 and 2002	Secretary, International Perinatal Doppler Society (IPDS)
1991-	Founding member of the International Society of Perinatal Obstetrician
1993-1995	Member of the Council, World Association of Perinatal Medicine (WAPM)
1993-	Member of the Board, International Society Fetus as a Patient
1996-	Member of the Board, International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)
1994-2000	Educational Committee (ISUOG)
1997-	Chairman, ISUOG Rapid Response Group

2000-	Scientific Committee (ISUOG)
2000-	President Elect (ISUOG)
1993-1997	Chairman, Working Group for Perinatal Medicine, Swedish Society of Obstetrics and Gynecology
1994-1996	President, Swedish Society of Perinatal Medicine
Editor:	1991-1998 International Editor, The Journal of Maternal-Fetal Investigation 1999 - Associate Editor for Europe, The Journal of Maternal-Fetal Medicine 1999 - European Deputy Editor of the Fetal Maternal Medicine Review
Member of the Editorial Board:	- International Journal of Obstetric Anesthesia (1992-1997) - Ultrasound in Obstetrics and Gynecology - Early Human Development - European Journal of Ultrasound - Czech Gynecology - Läkartidningen (1994-2000) - Kliniczna Perinatologia - Archives of Perinatology - Neuroendocrinology Letters - International Journal of Prenatal and Perinatal Psychology
Publications:	543 scientific publications in the field of Obstetrics and Gynecology, Perinatal Medicine, Fetal Physiology and Ultrasound (176 original papers, 99 chapters and reviews, 7 books, 241 abstracts, 20 miscellaneous publications)
Lines of research:	Research in the field of clinical obstetrics and perinatology, fetal medicine and fetal physiology (incl. animal experimental work), diagnostic ultrasound (incl. Doppler ultrasound), perinatal epidemiology.

RETRAINING PHASE AFTER INTERIM ANALYSIS AT SAHLGRENSKA UNIVERSITY HOSPITAL, GÖTEBORG

By Anna-Karin Sundström, Research Midwife

Before start of the Swedish randomized trial (autumn 1998) all midwives and obstetricians underwent training in intrapartum monitoring with ST analysis. The training consisted of a three hour lecture, and material was handed out for self learning. The lecture focused on basic physiology and interpretation of STAN recordings according to the teaching and training package made by Neoventa Medical. Everybody received a textbook covering the contents from the lecture. The multimedia version of the teaching and training package was installed on computers on site and also circulated among staff. The multimedia version covered the same issues as the textbook but also included a simulator where previously recorded cases with CTG and ST-analysis could be displayed. Before use of the monitor, all staff received a 15 minute demonstration of the STAN system. During the trial, the lectures were repeated in order to cover the needs of newly employed personnel. Approximately 120 midwives and 60 obstetricians were involved during the trial in Gothenburg.

The interim analysis, which was performed during the summer 1999, revealed that the study protocol was violated at several occasions. It was clear that some recordings from the hospital were not handled according to the study protocol, but based on traditional CTG interpretation only. This was true both for recordings with ST events that should have resulted in action and for recording with normal ST where no action should have been undertaken. In order to improve the situation, the study management group initiated the actions listed below:

1. Meeting with study managers and senior obstetricians. Information was given regarding protocol violations and the cases recorded at the labor ward were discussed. The meeting resulted in an improved support from those in charge.
2. Meetings with the staff members focusing on the cases and restating the trial purpose. There was no further training in basic physiology and CTG+ST data interpretation.
3. More frequent case discussions during the remaining trial, using cases obtained from the clinic.

We strongly believe that the improvement seen after the "retraining" was a result of several factors. At this point in time, most of the staff had experience monitoring with STAN, so the initial insecurity and tendency to manage matters in the old and well-known way would have been less. Also, to actually see traces from one's own ward and not from some other hospital may also have had an effect on the confidence in the method. Of course, the support from the opinion leaders at the department also played a role. The experience gained from the trial was that the best way to improve both recruitment for and compliance with the study protocol was the case discussions. Examples of these case discussions are included on the following pages.

EXAMPLES OF STAN RECORDINGS USED FOR DISCUSSION

OEB 282b

Date of delivery;

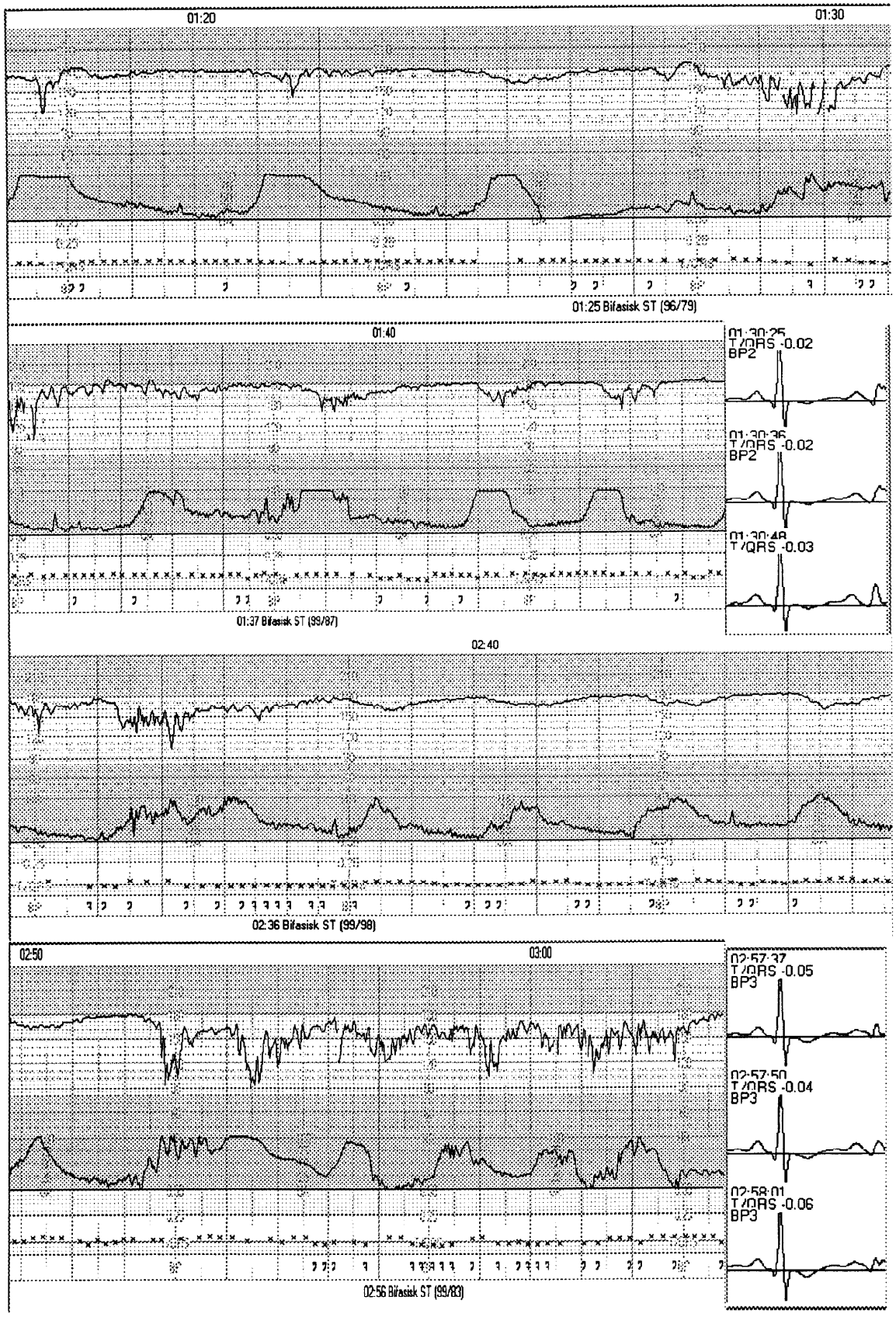
Clinical data
Para 0, 40 weeks of gestation, Normal pregnancy
Spontaneous onset of labour.
Meconium stained liquor.
FBS at 01:55; pH 7.30 and at 02:56; pH 7.34
Active pushing started 04:50
Mid cavity ventouse at 06:01 for FTP.

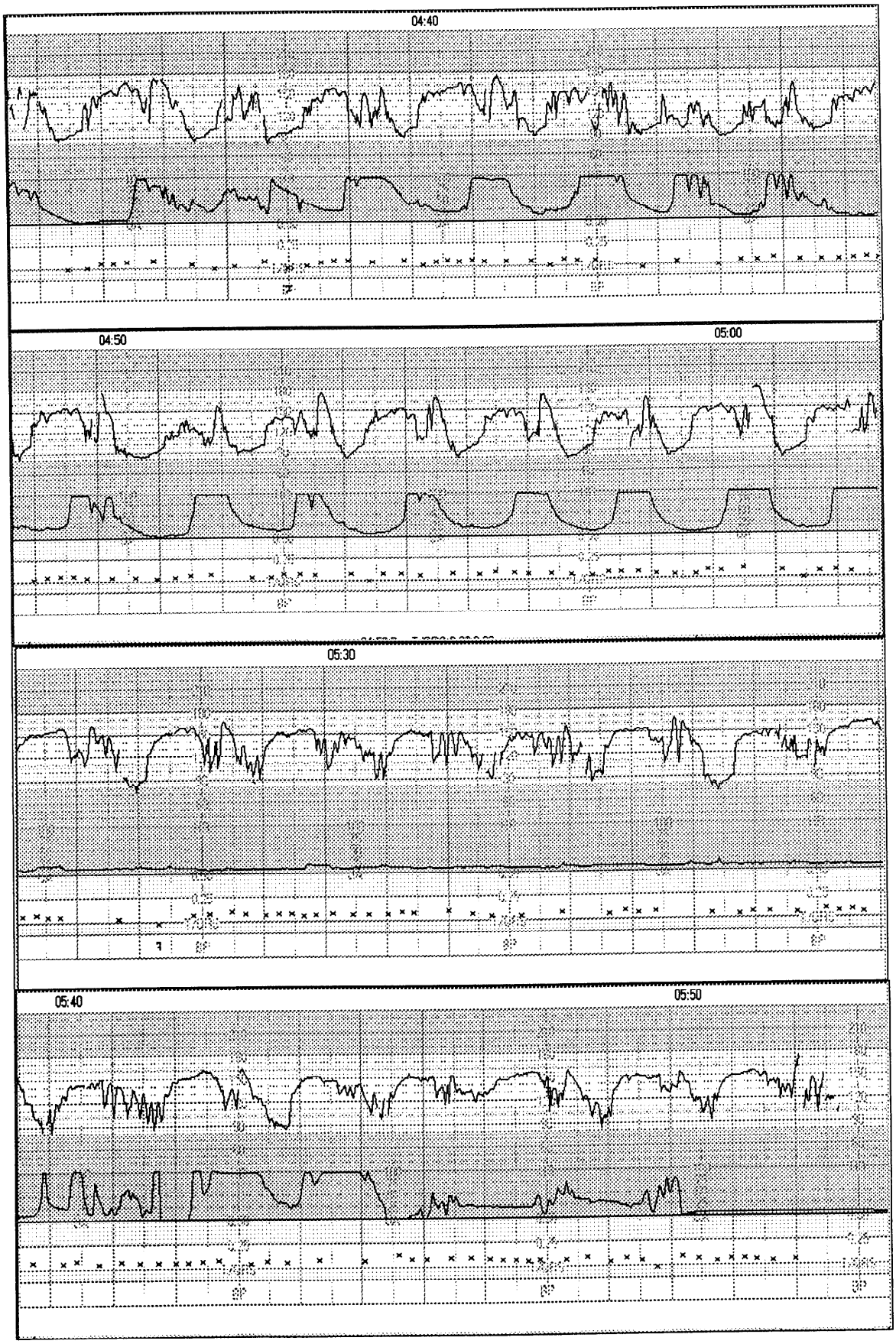
Neonatal data
Female 3770 g
Apgar 1-3-6
Cord artery: pH 7.03
PCO_2 6.17 kPa
BDecf 16.5 mmol/l

Cord vein: pH 7.04
PCO_2 6.38 kPa
BDecf 15.7 mmol/l
note same vessel – most likely cord vein.

Neonatal outcome
Initial resuscitation with face mask, extra O2, CPAP, cord artery catheter + buffer 30 ml.
Acid-base at 55 min of age: pH 7.04
PCO_2 3.12 kPa
BDecf 21.5 mmol/
Lactate 14.9 mmol/l
Glucose 10.4 mmol/l
At 6 hrs age deteriorating respiratory functions – meconium aspiration - on ventilator + surfactant treatment.
Normal neurology Day 1
Day 3 improving, off ventilator after 3 days
Normal neurology
Check-up 17 month of age: Everything normal.

Assessment of the recording
Good quality recording. Normal CTG+ST until 00:30 when baseline FHR increased to 180 bpm, from 00:50 shallow decelerations and at 01:25 first biphasic ST. This pattern continues with tachycardia, contraction induced decelerations and biphasic ST. From 04:30 marked late decelerations. At 04:40, a baseline T/QRS rise of 0.08 was noted. The recording finished at 05:52.


01:20
01:30
01:25 Bifasisk ST (96/79)
01:40
T/QRS -0.02
BP2
T/QRS -0.02
BP2
T/QRS -0.03
01:37 Bifasisk ST (99/87)
02:40
02:36 Bifasisk ST (99/98)
02:50
03:00
T/QRS -0.05
BP3
T/QRS -0.04
BP3
T/QRS -0.06
BP3
02:56 Bifasisk ST (99/83)


04:40
04:50
05:00
05:30
05:40
05:50

Comments
According to CTG+ST guidelines this should have been a cause of intervention.

OEH 330

Date of delivery;

Clinical data
Para 0, 40 weeks of gestation.
Normal pregnancy, spontaneous onset of labour, clear liquor.

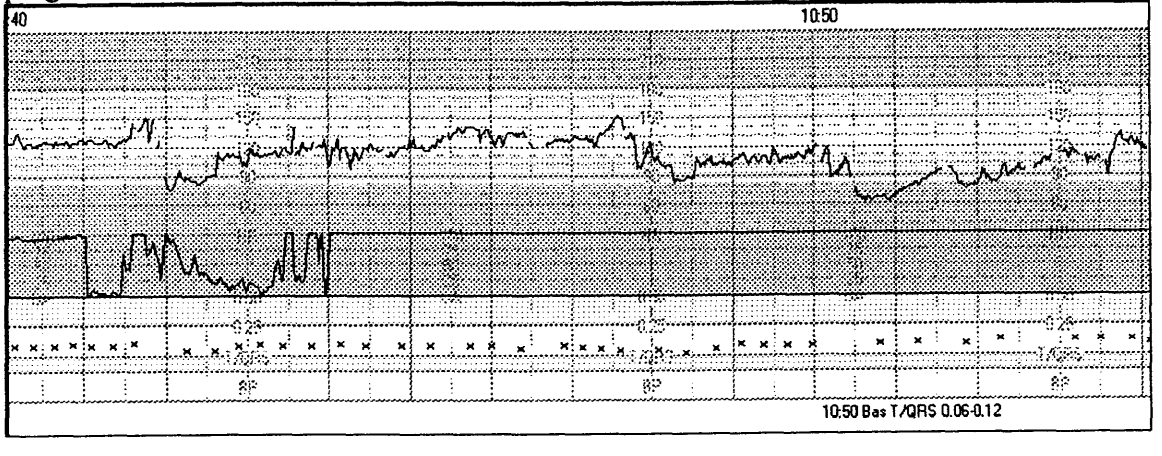
FBS at 10:16, pH 7.37.
Active pushing commenced at 11:15.
Mid cavity forceps 12:49 for threatening asphyxia.

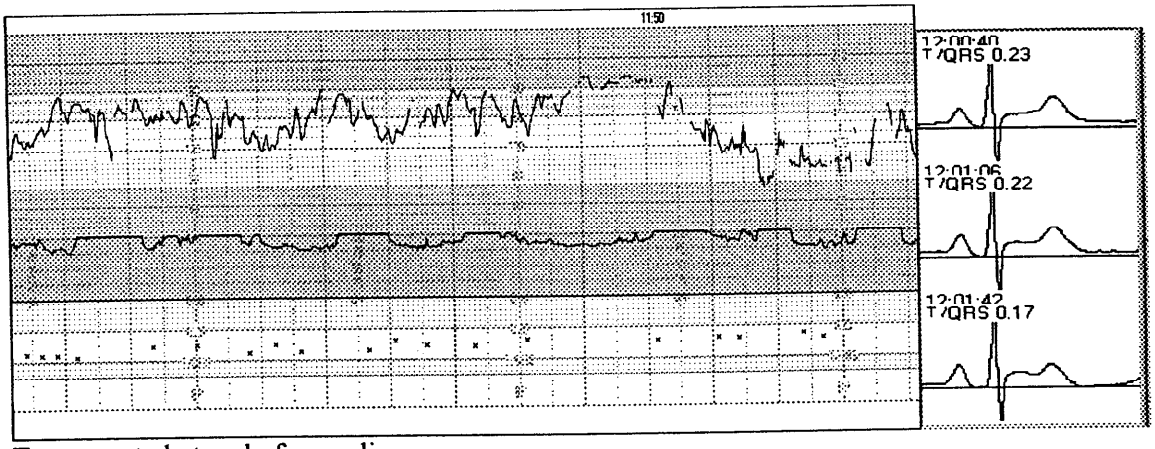
Neonatal data
Female 3530 g
Apgar 6-8-8
Cord artery: pH 6.88
PCO_2 11.73 kPa
BDecf 14.9 mmol/l

Cord vein: pH 6.97
PCO_2 9.10 kPa
BDecf 14.2 mmol/l

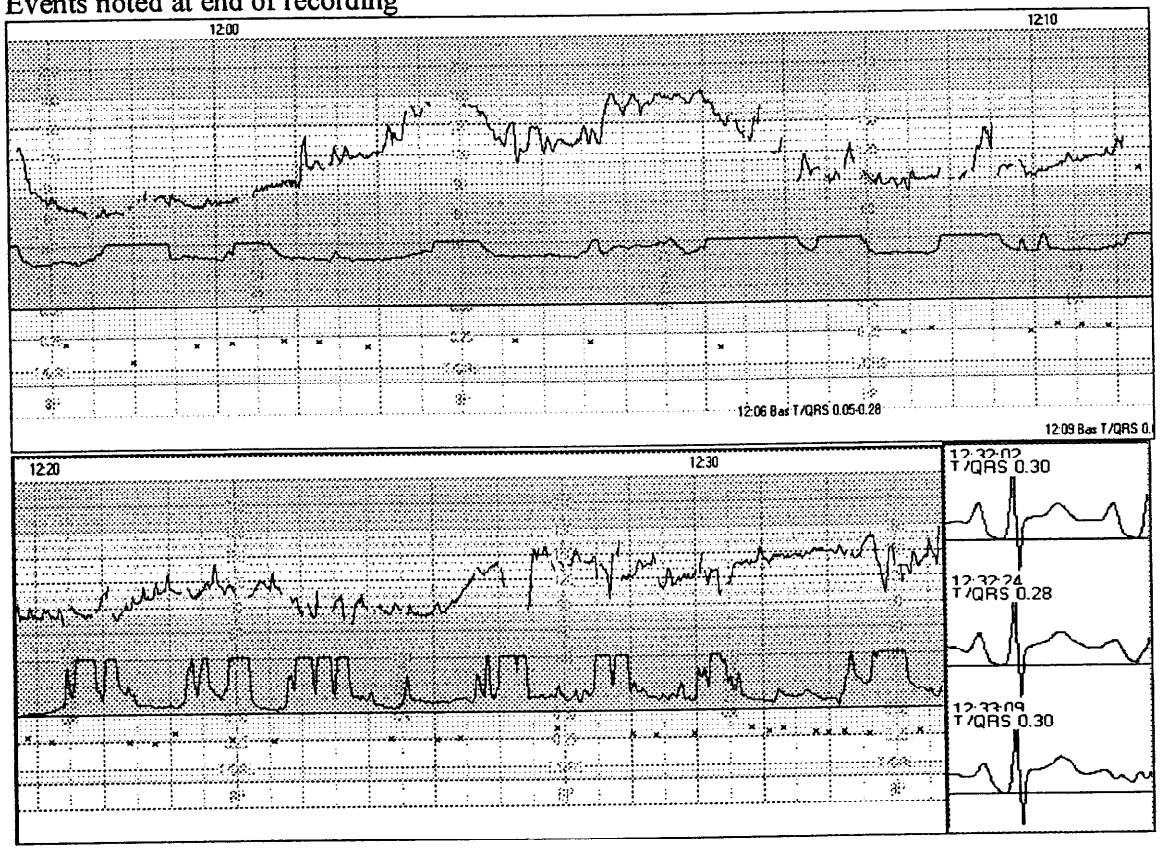
Neonatal outcome
15 ml buffer was given followed by normal acid-base findings.
General observation for one day without any signs of abnormal behaviour.

Assessment of the recording
Everything normal until 10:40. Bradycardia episodes with tachycardia in between, maintained short term FHR variability. First baseline T/QRS rise occurred at 10:50 followed by a progressive increase in T/QRS from 0.05 to 0.29 as 2nd stage progressed





Events noted at end of recording



Comments
CTG+ST clinical guidelines would have indicated a need for assisted delivery at 12:00.

OEB 239

Date of delivery;

Clinical data
Para 2, pyelonephritis during pregnancy spontaneous onset of labour after 39 weeks of gestation
Clear liquor

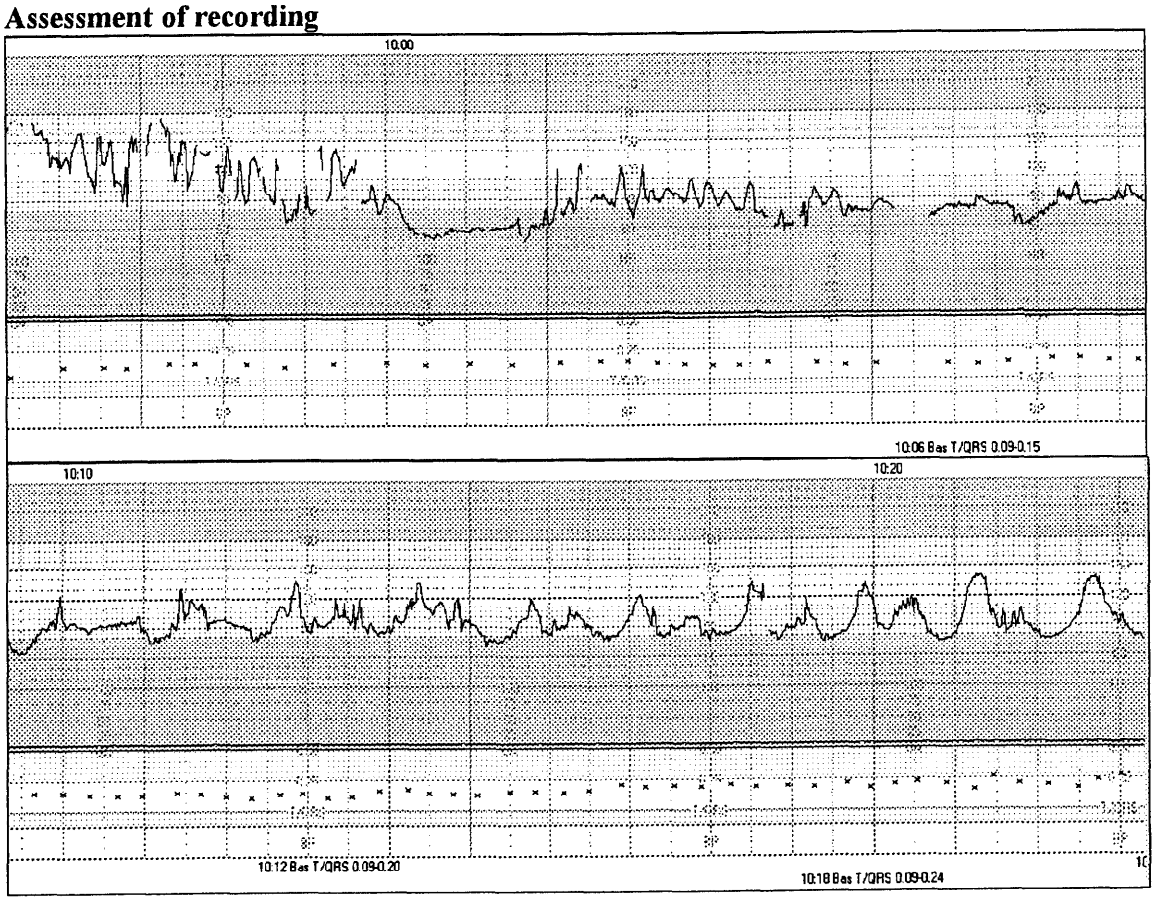
Active pushing commenced at 10:00

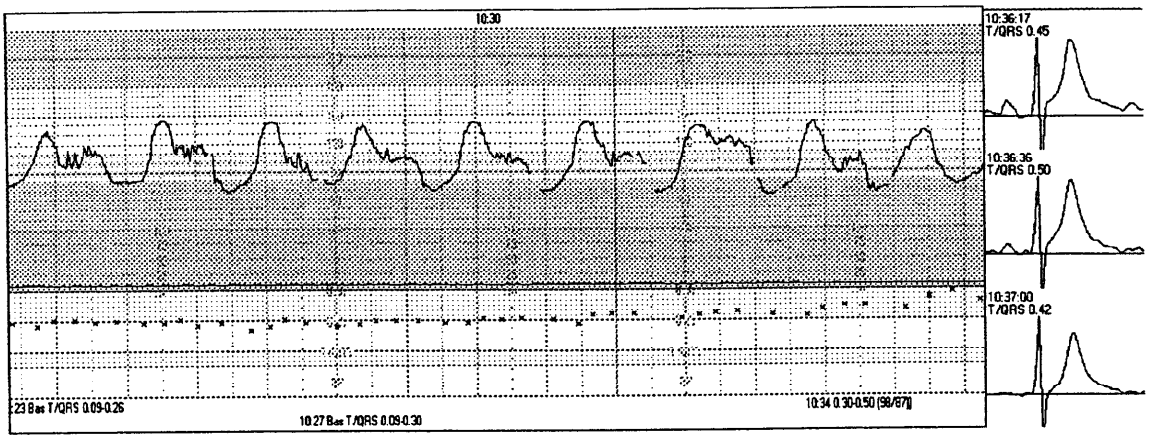
Normal vaginal delivery at 10:39

Neonatal data
Male 3600 g
Apgar 6-8-8
Cord artery: pH 6.87
PCO_2 12.61 kPa
BDecf 14.3 mmol/l

Neonatal outcome
Admitted to SCBU because of cyanosis, requiring 100% O_2. Normal neuromuscular status.
On ultrasound, signs of cardiac malformation with transposition + VSD + coarctatio.
Operated on at 2 month of age, nothing to indicate abnormal neurology at 18 month of age.

Assessment of recording





Normal CTG+ST until 09:50. At this point in time with onset of active pushing, the fetus reacted with increased short term variability followed by a bradycardia and a slow recovery of baseline FHR. This event was followed by intermittent decelerations with graded loss of short-term variability. End of recording at 10:37. Note, the uterine activity sensor had been disconnected.

Comments
According to CTG+ST clinical guidelines, an assisted operative delivery should have commenced approx. 10:10.

Oed0232

Date of delivery,
Clinical data
Para 0, essential hypertonia, augmented labour after 40 weeks of gestation due to PROM. Clear liquor

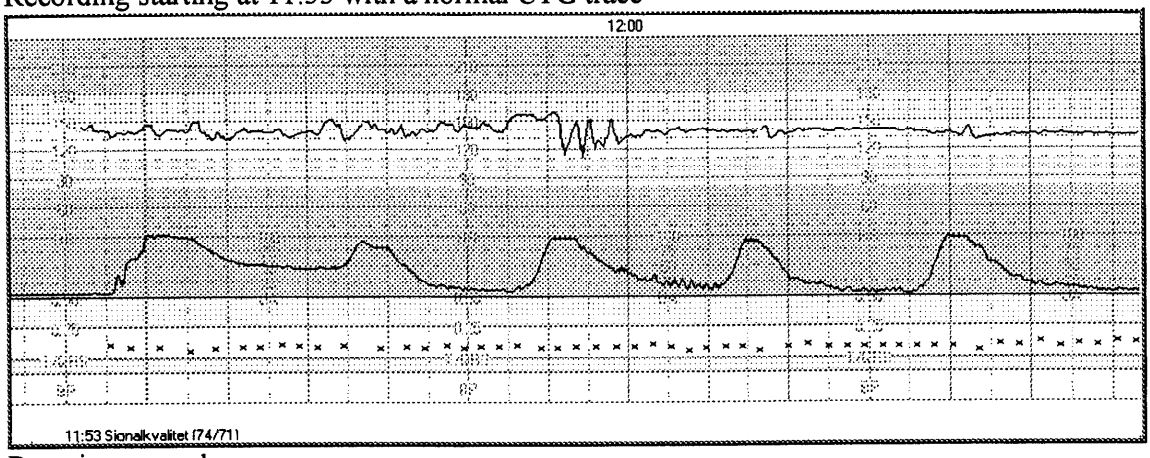
Active pushing commenced at 18:10
Outlet ventouse, time of birth 18:58

Neonatal data
Female 3190 g
Apgar 1-6-7
Cord artery: pH 7.07
PCO_2 6.85 kPa
BDecf 13.5 mmol/l
Cord vein: pH 7.16
PCO_2 6.11 kPa
BDecf 10.8 mmol/l

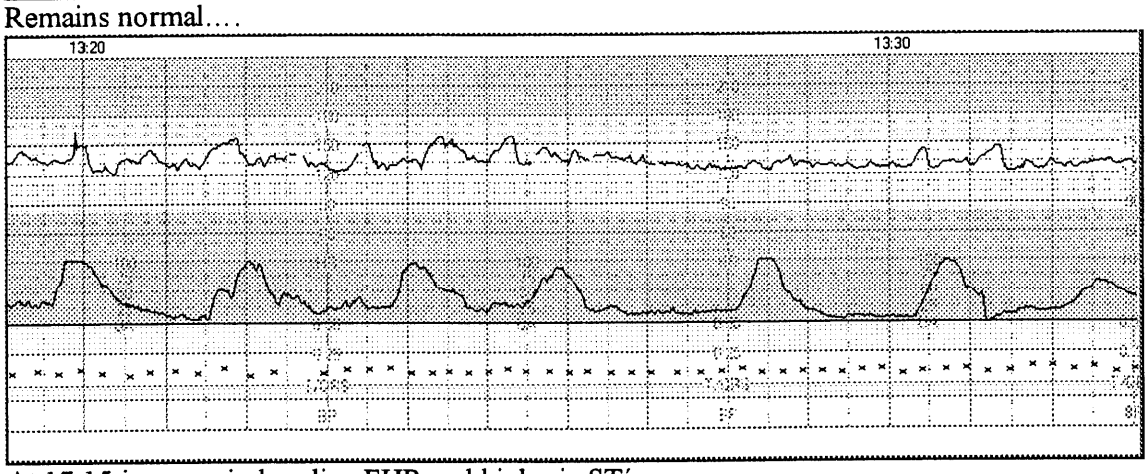
Neonatal outcome
Admitted to SCBU

Assessment of recording

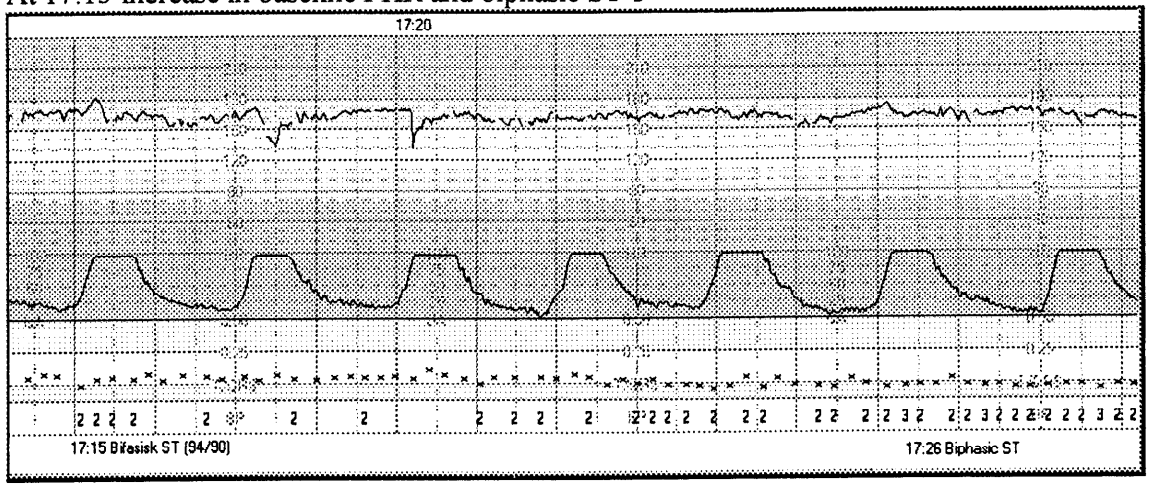
Recording starting at 11:53 with a normal CTG trace



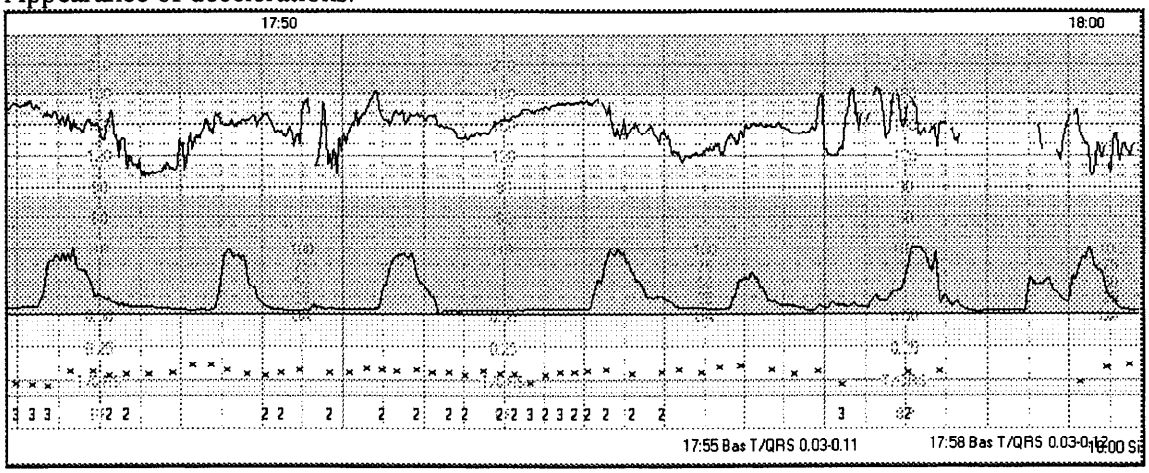
Remains normal....



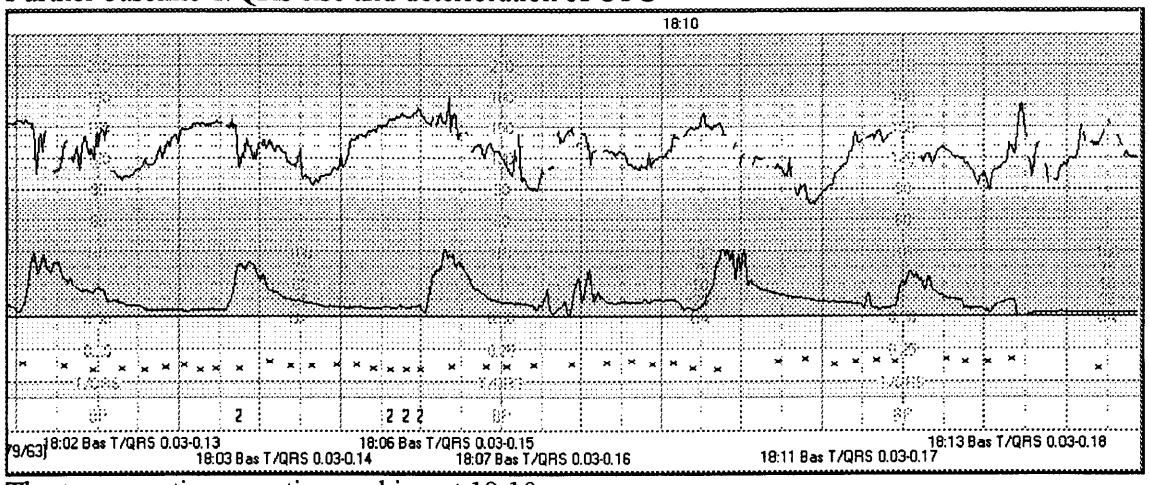
At 17:15 increase in baseline FHR and biphasic ST's



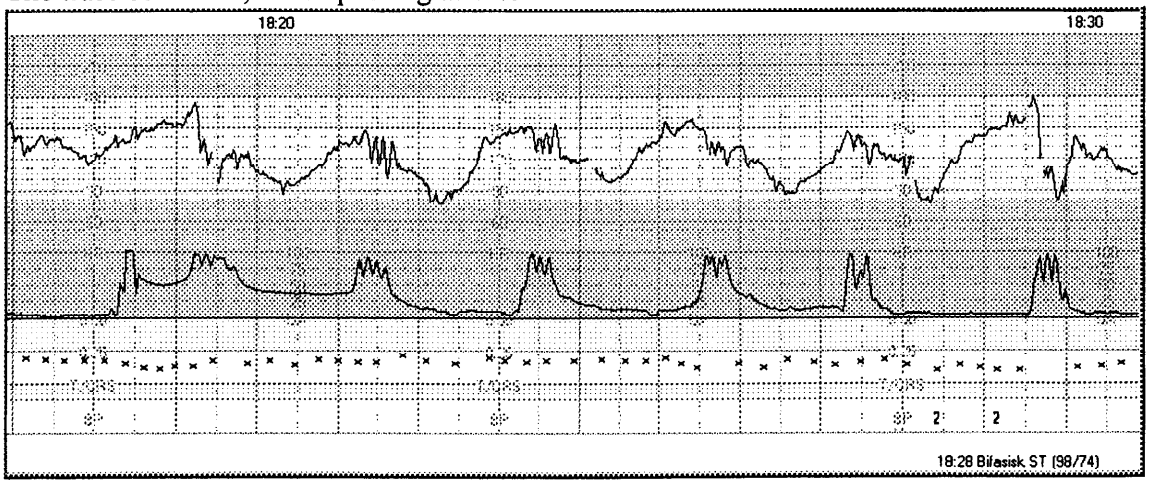
The trace is showing biphasic STs during 40 min, now shifting to a baseline T/QRS rise. Appearance of decelerations.



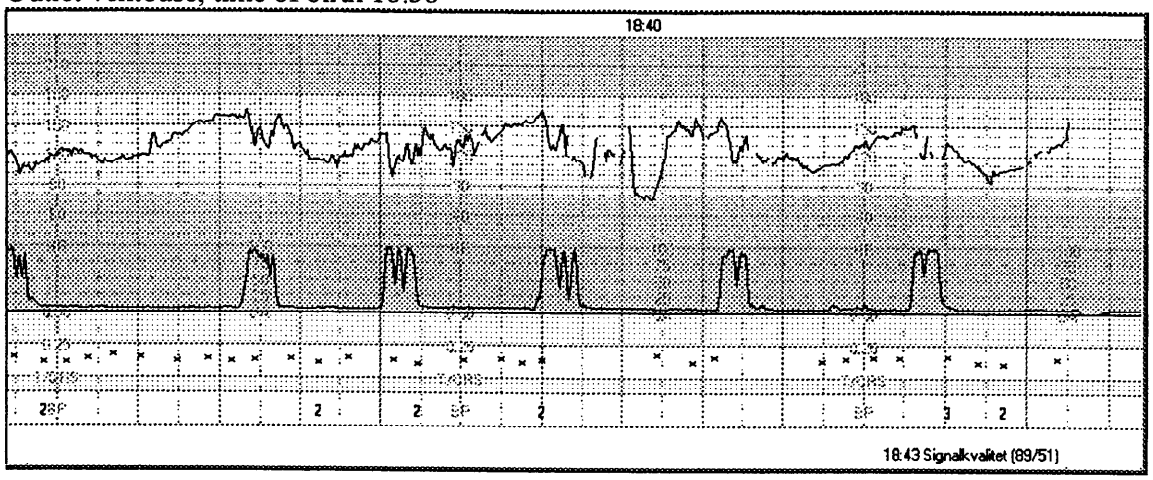
Further baseline T/QRS rise and deterioration of CTG



The trace continues, active pushing at 18:10



Outlet ventouse, time of birth 18:58



Comments
According to CTG+ST clinical guidelines, an assisted operative delivery should have commenced approx. 17:50.

OEE 221

Date of delivery;

Clinical data
Para 0, 41 weeks, suspected growth retardation and oligohydramnios, augmentation of labour, meconiumstained amniotic fluid.

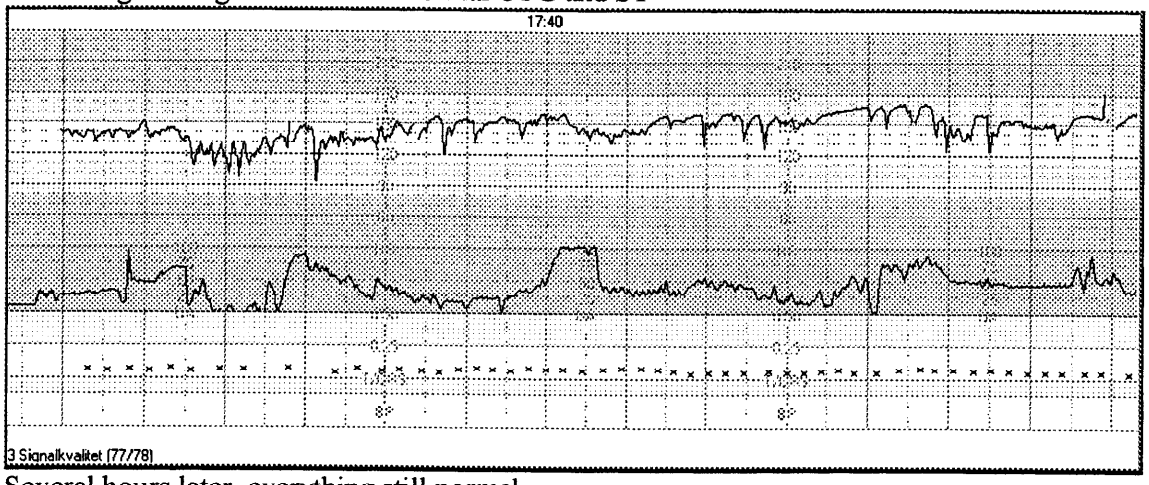
Active pushing commenced at 02:40
Normal vaginal delivery at 03:18

Neonatal data
Female 2935 g
Apgar 1-2-9
Cord artery: pH 6.99
PCO_2 10.88 kPa
BDecf 10.4 mmol/l
Cord vein: pH 7.05
PCO_2 9.37 kPa
BDecf 9.7 mmol/l

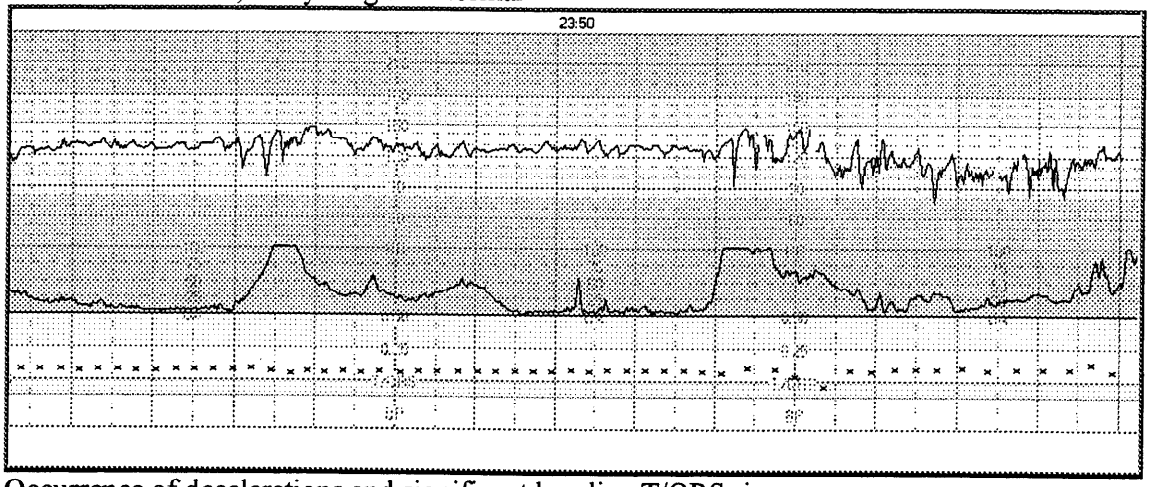
Neonatal outcome
Admitted to SCBU.

Assessment of recording

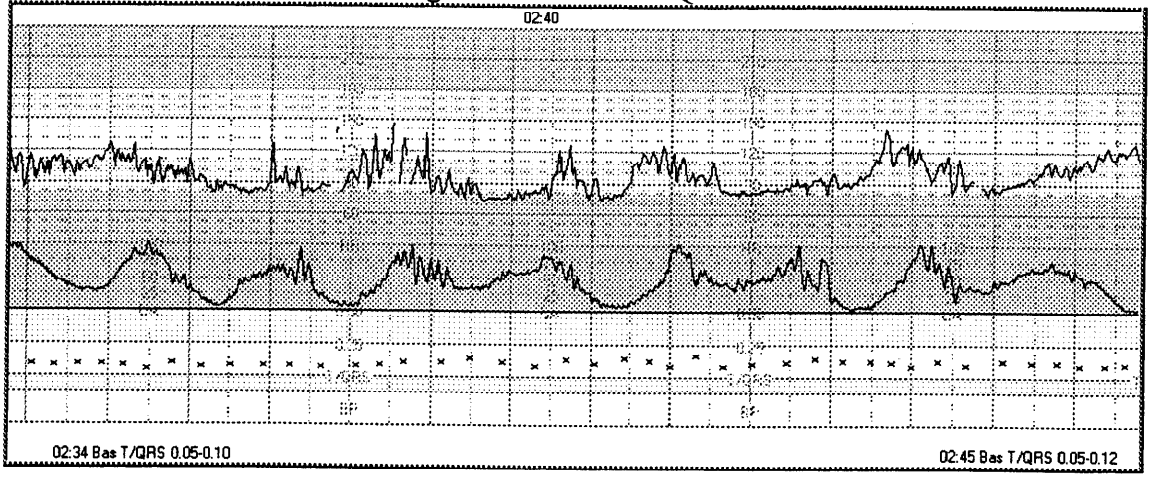
Recording starting at 17:34 with normal CTG and ST



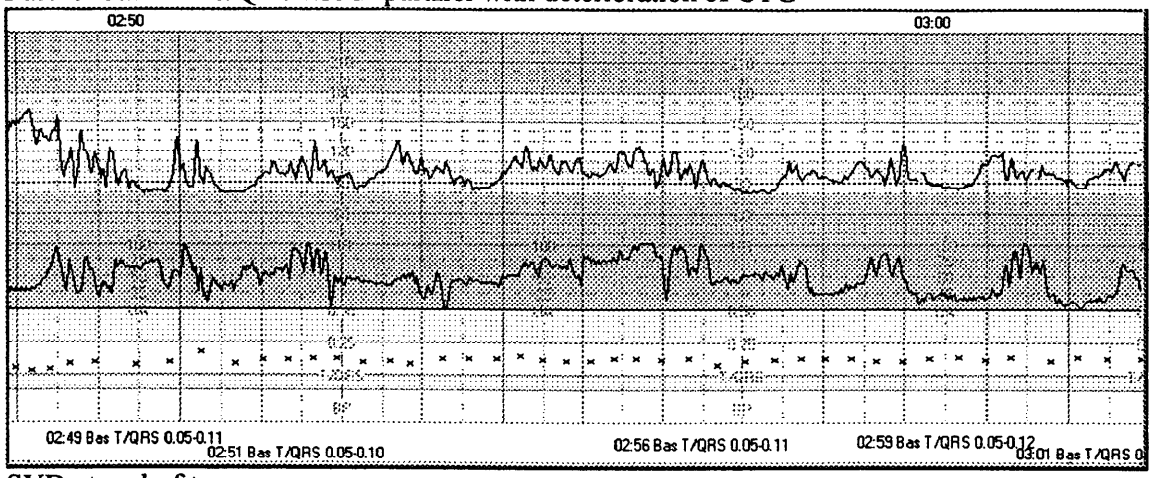
Several hours later, everything still normal



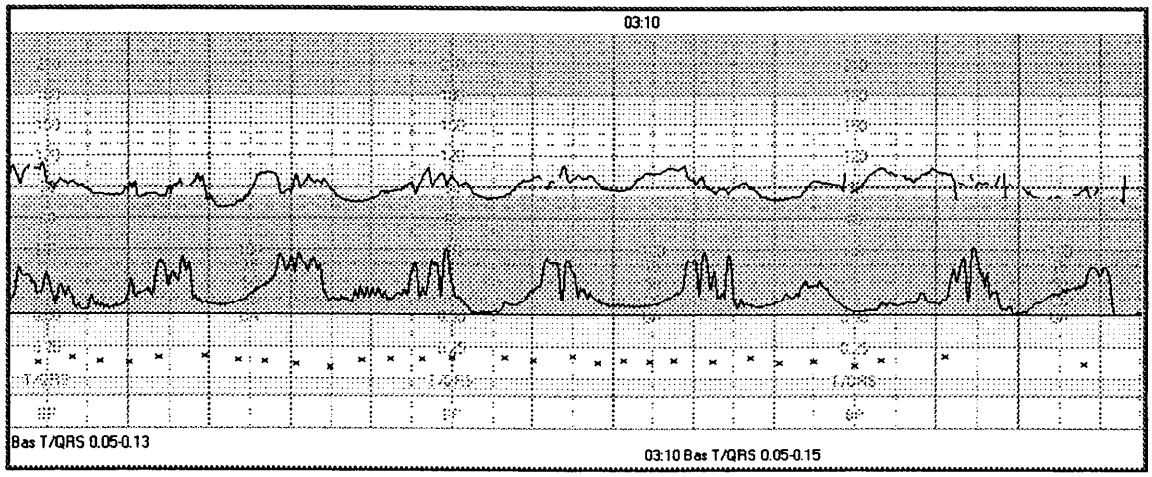
Occurrence of decelerations and significant baseline T/QRS rise



Further baseline T/QRS rise in parallel with deterioration of CTG



SVD at end of trace



Comments
According to CTG+ST clinical guidelines, an assisted operative delivery should have commenced approx. 02:45.

Oek0235

Date of delivery,
Clinical data
Para 1, 42 weeks, augmentation of labour.
Clear liquor

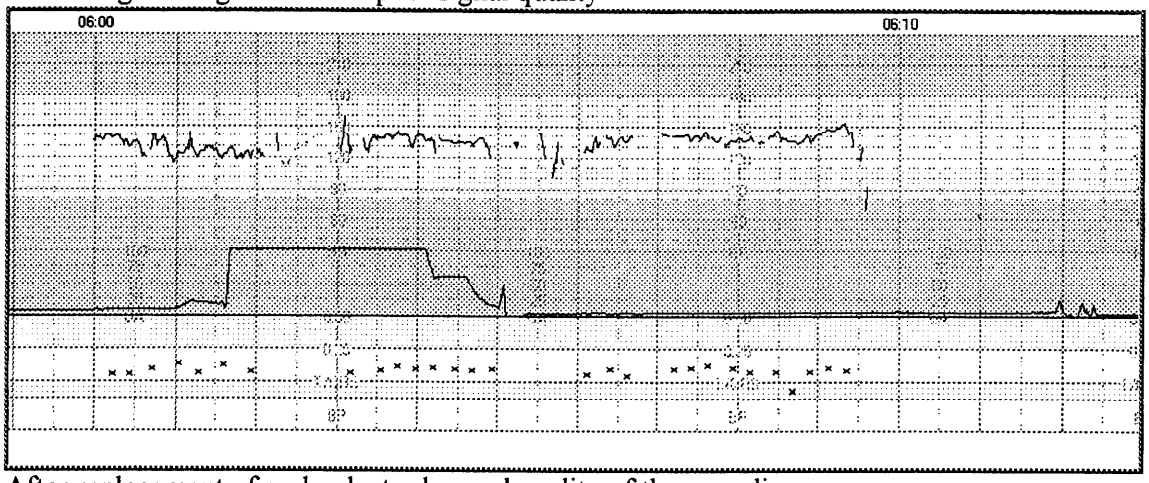
Active pushing commenced at 11:20
SVD, time of birth 11:31

Neonatal data
Male 3975 g
Apgar 9-10-10
Cord artery: pH 7.19
PCO_2 7.62 kPa
BDecf 5.4 mmol/l

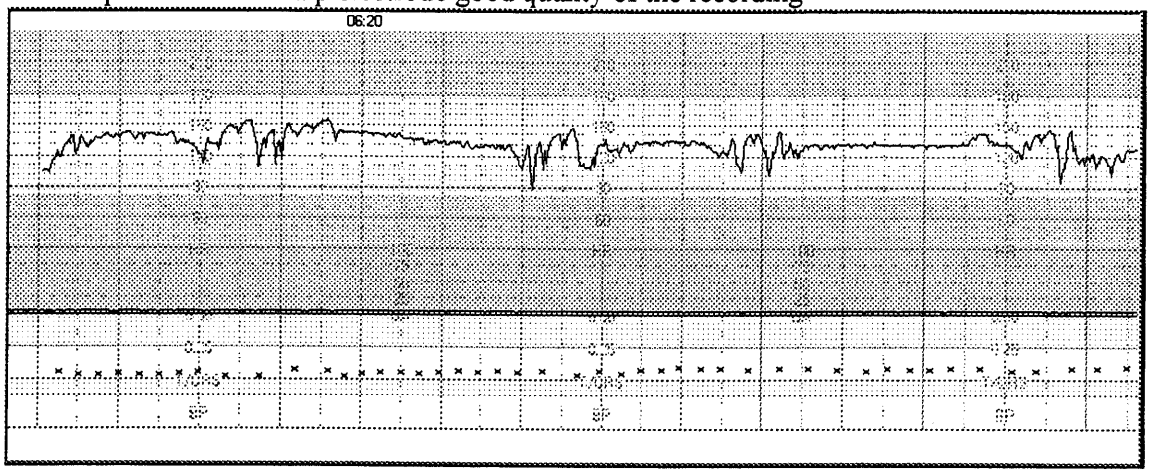
Cord vein: pH 7.27
PCO_2 6.18 kPa
BDecf 4.7 mmol/l

Neonatal outcome
Normal neonatal period

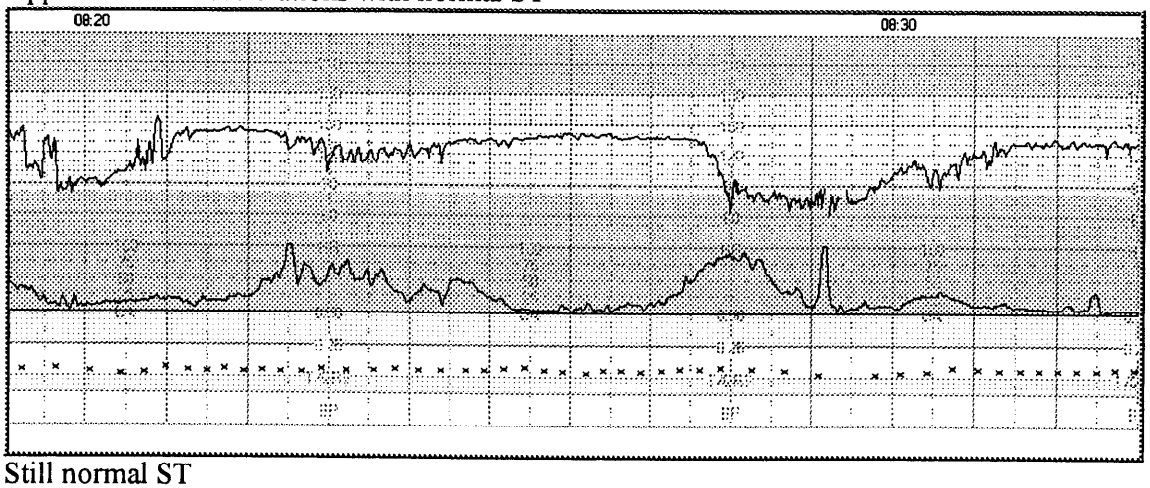
Assessment of recording
Recording starting 06:00 with poor signal quality



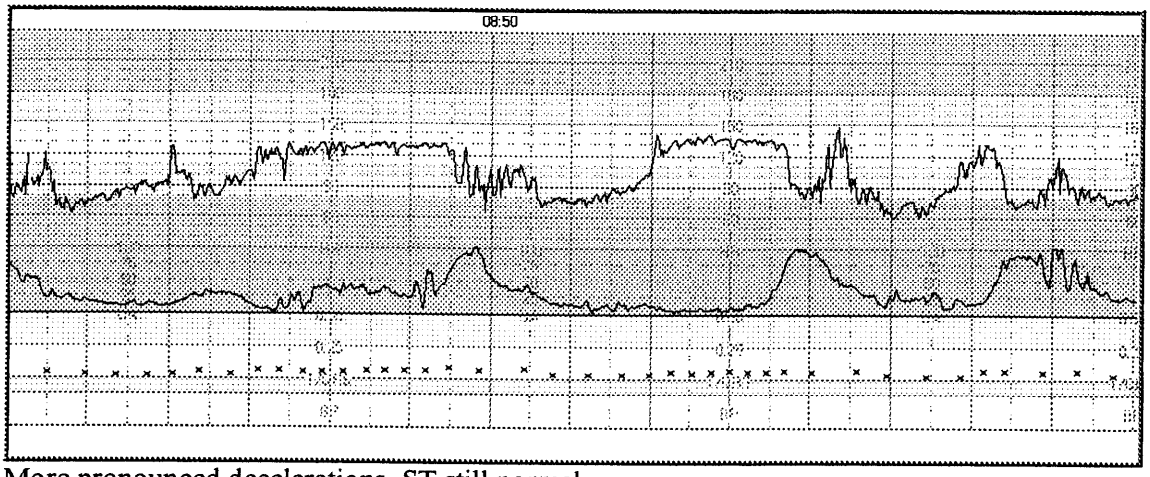
After replacement of scalp electrode good quality of the recording



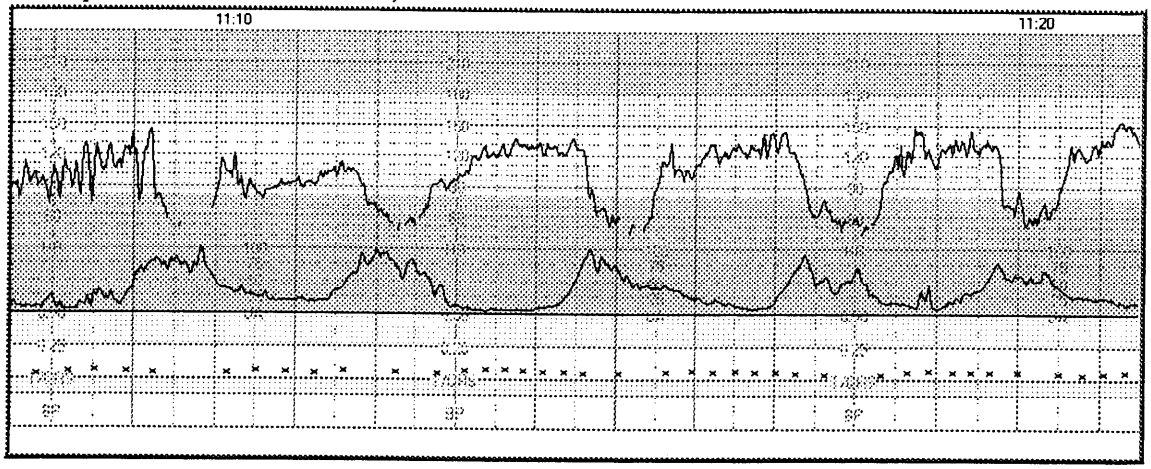
Appearance of decelerations with normal ST



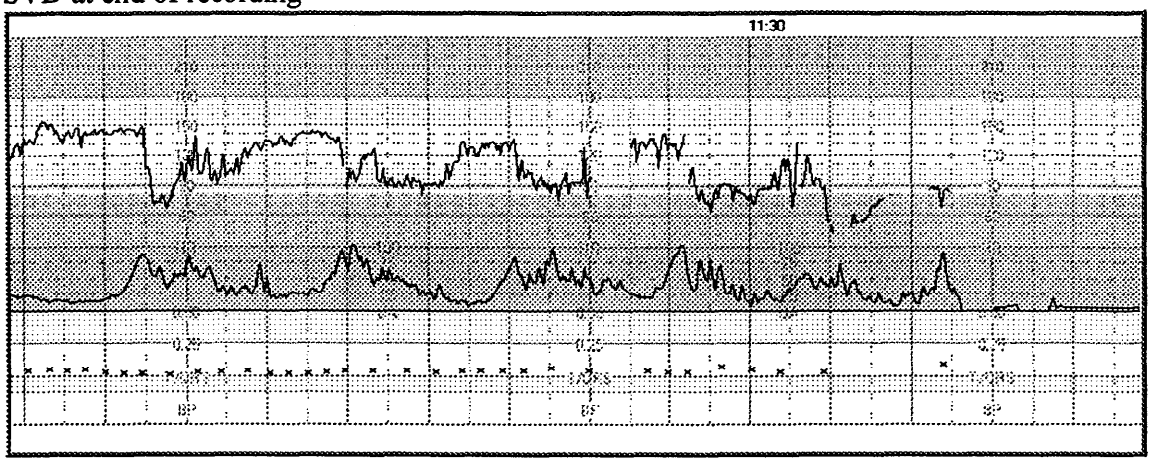
Still normal ST



More pronounced decelerations, ST still normal



SVD at end of recording



Comments
A case that was handled according to the study protocol.

Oej0281

Date of delivery,

Clinical data
Para 1, 39 weeks, gestational diabetes and preeclampsia, augmentation of labour.
Clear liquor

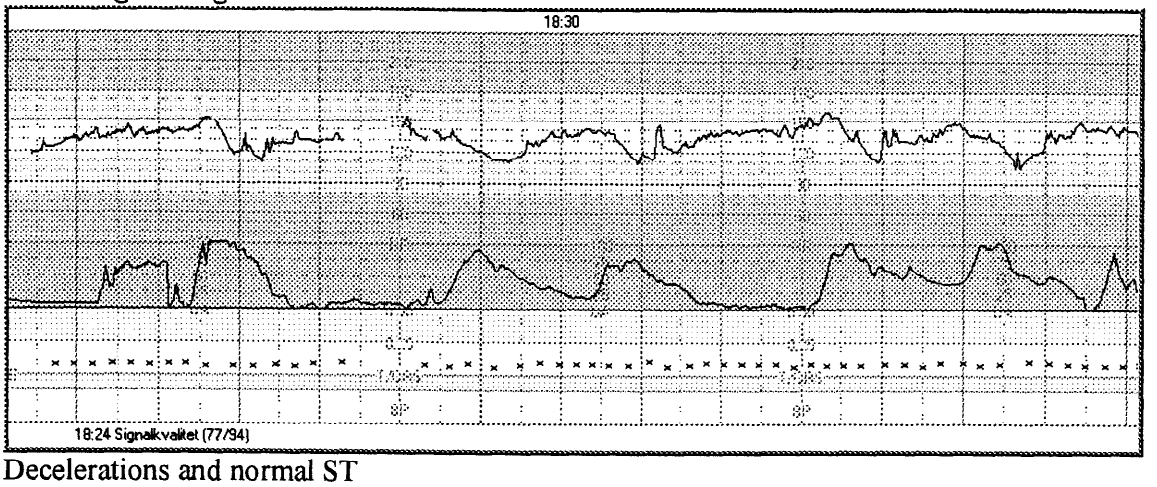
CS, time of birth 22:38

Neonatal data
Male 3770 g
Apgar 7-10-10
Cord artery: pH 7.26
PCO_2 7.15 kPa
BDecf 2.4 mmol/l
Cord vein: pH 7.29
PCO_2 6.43 kPa
BDecf 2.7 mmol/l

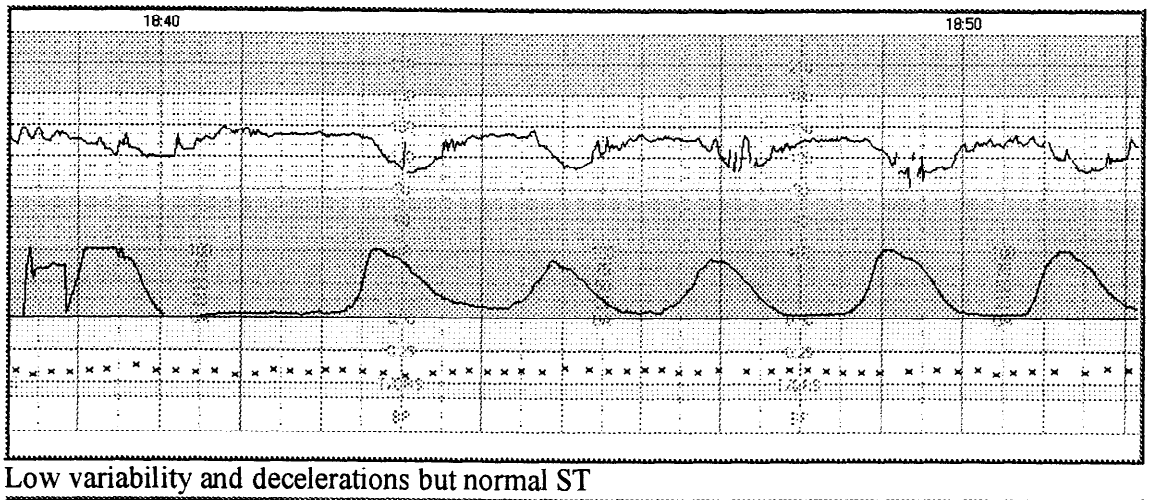
Neonatal outcome
Normal neonatal period

Assessment of recording

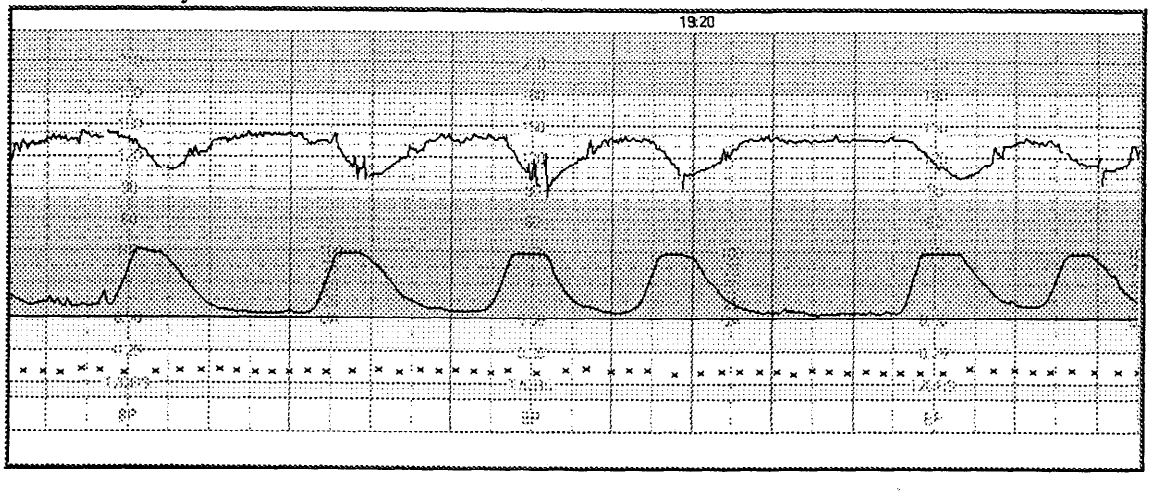
Recording starting at 18:23



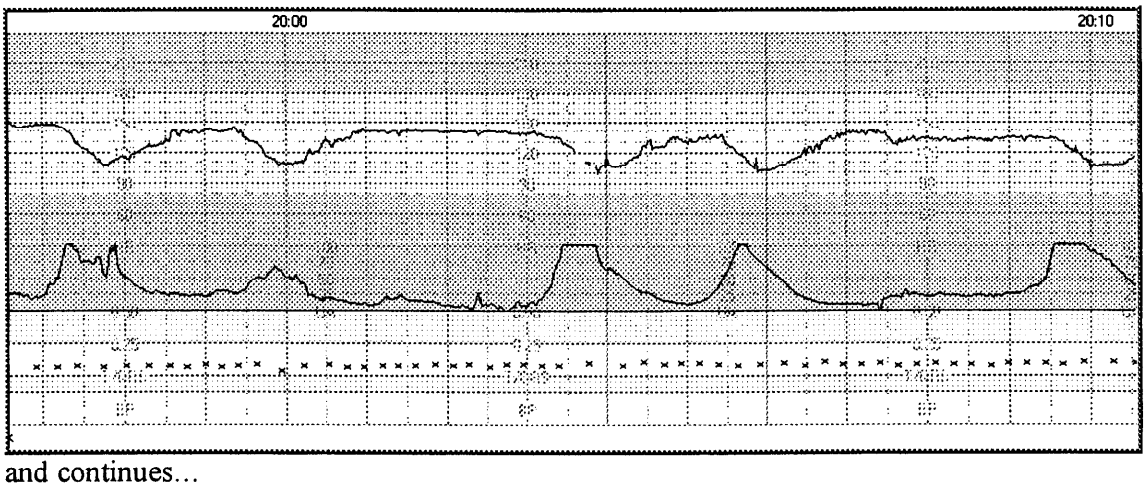
Decelerations and normal ST



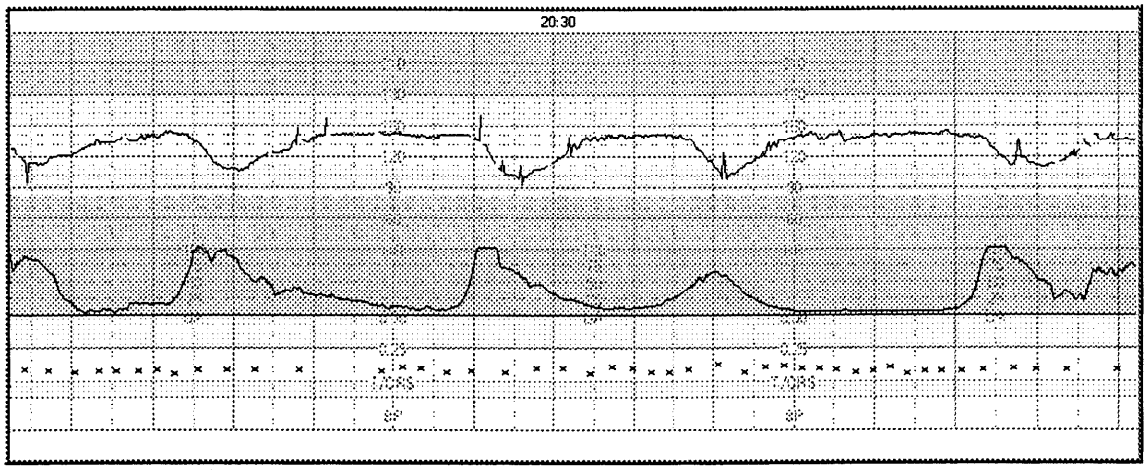
Low variability and decelerations but normal ST



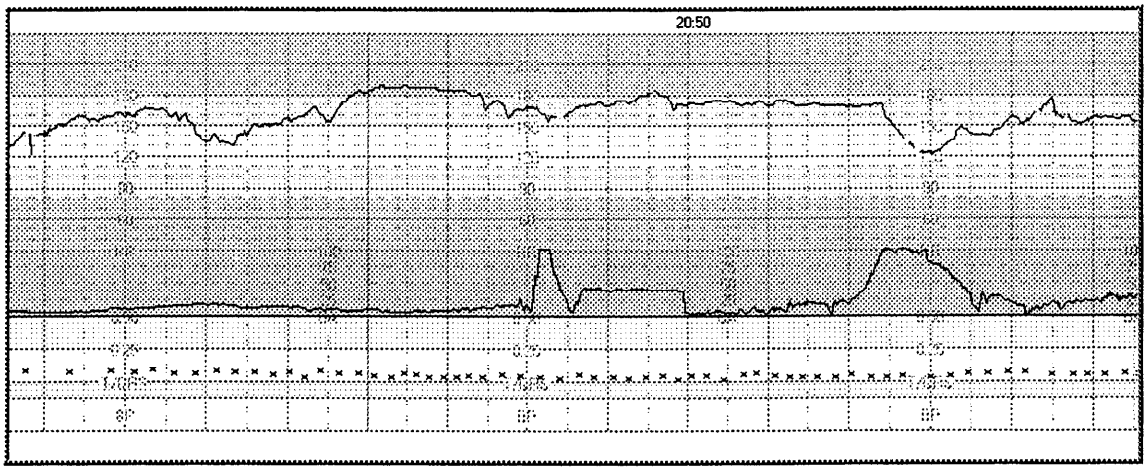
The case continues....

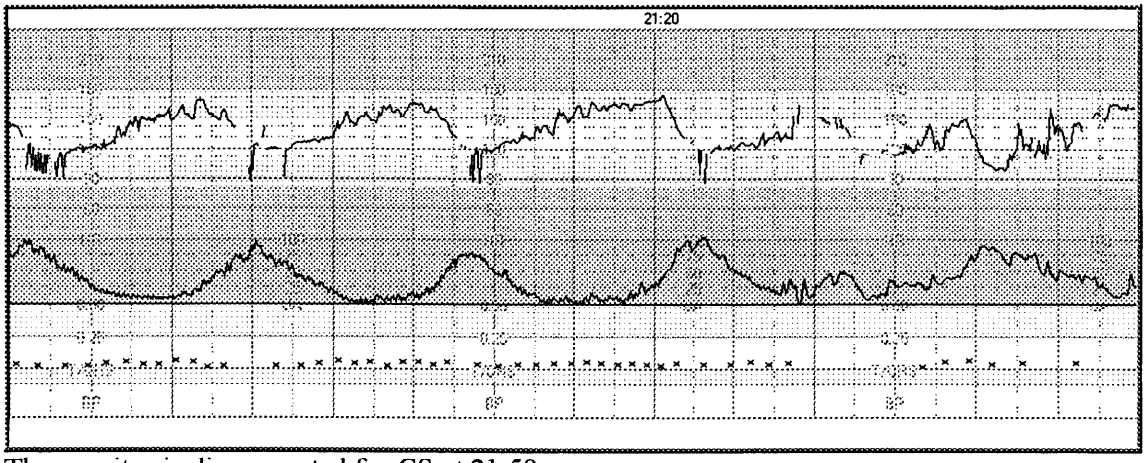


and continues...

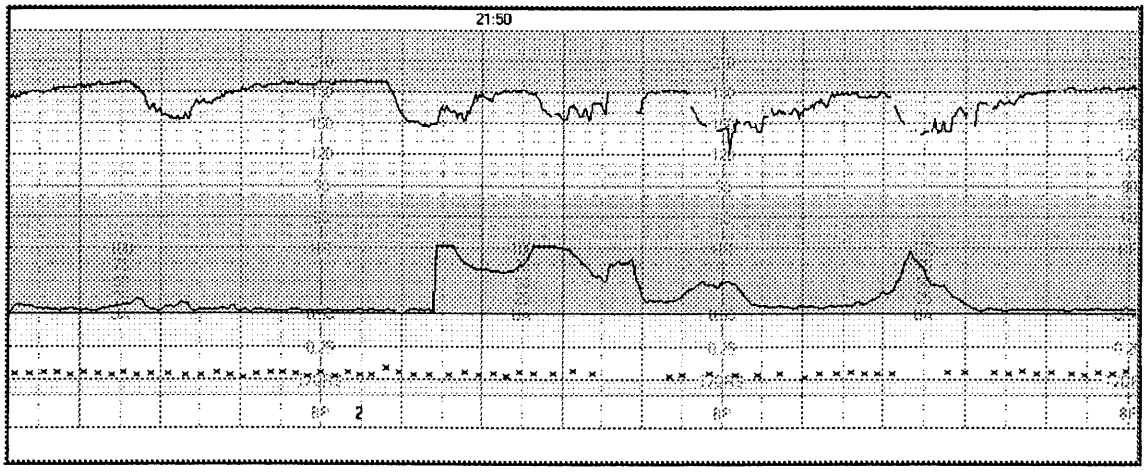


ST is still normal





The monitor is disconnected for CS at 21:58



Comments

A recording showing long-lasting CTG abnormalities but a normal ST indicating that the fetus is in control.